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BEHAVIOR DISORDERS ASSOCIATED WITH INTRACRANIAL TUMORS IN CHILDHOOD

REPORT OF CASES

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In the past five years 3 of the children referred to the pediatric psychiatric clinic of the Babies Hospital were discovered to have intracranial tumors. The study of these patients aroused our interest in the general subject of mental symptoms, personality changes and behavior disorders in children with intracranial tumors.

It has been said that mental symptoms with tumors of the brain occur less frequently in children than in adults. Ford [1] pointed out that the progression to paralysis and death is usually so rapid that the effect on the mental condition is rarely stressed. He further said that if the location of a neoplasm is such that serious disability does not occur early mental symptoms may be prominent at first, the usual observation being of a simple dementia without striking changes in behavior. Listlessness and loss of interest in the normal occupations of play and school work along with fretfulness and irritability are often present. These symptoms are so frequently encountered among children that little attention may be given them until the dulness, lethargy and somnolence associated with increasing intracranial pressure come to the fore. There have been few studies of the mental symptoms accompanying tumors of the brain in childhood. Bailey, Buchanan, and Bucy [2] in a study of 100 children with intracranial tumors did not find that mental symptoms were outstanding. Critchley [3] in an analysis of 125 cases did not feel that they were of use in localization. He found altera-

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1. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood, and Adolescence, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 933.

2. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

3. Critchley, M.: Brain Tumors in Children: Their General Symptomatology, Brit. J. Child. Dis. **22**:251-264 (Oct.-Dec.) 1925.

tions in disposition, listlessness, mental and emotional dulness and lethargy, becoming more marked with the increase in intracranial pressure, to be common. He said that psychomotor restlessness, excitement and delirium were not seen, although Bailey and his associates observed several cases with delirium or in which the patient did or said foolish things. In these cases there was associated involvement of the hypothalamus. Keschner, Bender and Strauss [4] described the mental changes in a group of 120 patients with subtentorial tumors; 37 of these were children under 14 years of age. In this group of children the incidence of psychic symptoms was 25 per cent less than in the adults and they were less complex. Approximately one third of the children showed mental changes of one sort or another. Nine showed changes in the nature of apathy, dulness, somnolence, poor cooperation or inattention of a mild and transitory nature. Apprehension and depression were noted, as well as excessive crying and temper tantrums. The last-mentioned symptoms were thought to be reactions to a severe illness and not specific. Euphoria was noted in one child. Five were said to have shown personality changes, the nature of which was not specified. The basis of this observation was that their familiars stated that they were "different persons."

It is not unusual for the symptoms of an intracranial tumor to be looked on as a functional behavior disorder early in the course of the disease. The vomiting, an exceedingly common symptom in childhood, is not infrequently at first diagnosed as cyclic or psychogenic vomiting or attributed to gastrointestinal disorder. The vomiting is often enough precipitated by an acute febrile illness, an operation or a mild head injury. Bailey and his associates found that pertussis was the most common offender. The tendency of the early vomiting and headache to disappear after a few days or a week or two only to reappear at a later date is also confusing. They pointed out that despite the fact that the most common form of vomiting in cases of intracranial tumors is accompanied by persistent, and at times extreme, nausea, physicians are still taught that the vomiting is forceful, sudden in onset and without nausea. It is apt to be unrelated to the ingestion of food. Persistent anorexia is rarely observed. In most of the cases in which there has been an error in diagnosis, the rapid appearance of neurologic signs and of evidence of increasing intracranial pressure causes apprehension in the attendants and the true nature of the condition becomes apparent.

We have been able to find in a cursory search descriptions of only 2 cases in which there was a behavior disorder associated with intracranial neoplasm. In both of these as well as in our own cases, physical

4. Keschner, M.; Bender, M. B., and Strauss, I.: Mental Symptoms in Cases of Subtentorial Tumors, Arch. Neurol. & Psychiat. **37**:1-18 (Jan.) 1937.

signs were conspicuously absent when the patient was first seen, although the child himself was obviously disordered.

In 1937 Roback [5] commented on the rarity of reports of behavior disorders in children with tumors of the brain. He summarized the history of a girl who presented a behavior disorder associated with a tumor involving the left frontal and temporal lobes. She was first seen in 1930, at the age of 7 years. Her illness had begun at the age of 5, when, shortly after a fall, she had begun to have mild convulsive attacks of a petit mal type. These attacks persisted until she was operated on, at the age of 12 years. They would practically disappear when she was in the hospital or when she was away from home. When she was 10 years of age there were a few neurologic signs but not enough to warrant the diagnosis of a tumor. Along with the convulsive attacks she showed a mild, yet definite, change in her personality. She became irritable, stubborn and disobedient. It was only with threats of punishment, which she dreaded, that she could be gotten to do her household chores or her school work. At school she had outbursts of temper and slammed her books on the desk when asked to do things. She had to do things hastily and to have what she wanted. She wished to be babied, wanted to sit on her mother's lap and objected to being alone at any time. She became jealous of her older sister, quarreled with her and resented any attention given to the sister. She was extremely active and preferred to play with children who were boisterous and rough. Her intelligence quotient fell from 125 to 104 between 1930 and 1932. After the removal of a protoplasmic astrocytoma in January 1935 her seizures gradually disappeared and at last report her behavior had shown considerable improvement.

Keschner, Bender and Strauss,[4] also in 1937, mentioned an 8 year old girl who in August 1932 began to brood after her family had moved from the house where she had grown up to another part of the city and had not gone to the country for a summer vacation. She kept asking to be taken back to her former home. In September 1932 she began to vomit every morning. Between bouts of vomiting she was surly and reproached her family for having moved. As the day wore on she would become more cheerful and complacent. One month later she began to have severe headaches and became more irritable and moody. In December she was admitted to the hospital and remained eight days. During this period she was always depressed and cried a great deal. She blamed her mother and sister for her condition, which she attributed to the change in residence. She also vomited frequently and complained of headache. Psychometric examination revealed that she was of superior intelligence. Because of the absence of physical

5. Roback, H. N.: Behavior Disorder Associated with Brain Tumor, Bull. Menninger Clin. **1**:91-96 (Jan.) 1937.

signs of organic disease she was thought to be suffering from a psychoneurosis and was referred for psychotherapy. Two weeks after her discharge from the hospital she died as a result of an automobile accident. Autopsy revealed a medulloblastoma of the vermis.

Because of the infrequency with which personality and behavior disorders associated with intracranial neoplasms in children have been reported, it seemed that it would be of interest to present in some detail our 3 cases, even though the psychiatric investigations done were not extensive. Schilder [6] pointed out the artificiality of considering isolated mental symptoms and the real need to describe the psychologic and psychiatric symptoms from the point of view of the personality change and of what is going on in the patient. The personality cannot be separated from the clinical picture. He felt that much could be learned of the nature of symptoms and localization if patients with tumors of various sites could be studied psychiatrically in the way in which patients with neuroses and functional psychoses are studied.

REPORT OF CASES

CASE 1.—Helene L., a Jewish girl of 8 years, 8 months, was first seen Oct. 5, 1936, having been referred for psychiatric treatment by the pediatric service of another hospital.

Her illness had begun about the first of May, five months before. She had been well since the age of 4 years. She had been pleasant and sociable, with many friends with whom she liked to play. There had always been a mild feeding problem; she ate little breakfast and had had many food dislikes. At this time definite anorexia developed and she ate only after considerable urging. Along with this she became irritable, began to dislike going out with her friends, "crawled into her shell," and showed considerable jealousy toward her younger sister, aged 4 years. She felt that her sister got everything at home. She began to demand that her mother do everything for her and said that her mother no longer loved her. The anorexia increased, and about the middle of June, six weeks after the onset, she began to vomit. At first she would vomit at lunch time on her return home from school. The vomitus consisted of the undigested previous meal. The frequency increased to three or four times a day, usually just before meals. Irritability, stubbornness and difficulty in management increased. She became restless and "nervous"; she bit her fingers incessantly and picked at her toes and lips. She had lost 4 pounds (1.8 Kg.) at the time of her admission to another hospital, June 29, 1936.

She remained in that hospital a month. Physical examination showed nothing remarkable aside from evidence of mild recent loss of weight. The eyegrounds were normal. The spinal fluid was said to be under "normal" pressure, although manometric studies were not done. An extensive laboratory work-up revealed nothing helpful. The vomiting and loss of appetite became more pronounced in the hospital. She vomited from two to five times a day, just before meals, during meals, after meals and between meals. Because of the definite increase in symptoms and further loss of 9 pounds (4 Kg.), she was sent home. The discharge diagnosis was psychogenic vomiting. She was followed closely until referral to us.

6. Schilder, P., in discussion on Keschner, Bender and Strauss.[4]

While in the hospital she was noted to be listless and to appear unhappy. She complained of her younger sister's getting everything at home. She wrote her mother a note asking her if she was heartbroken about the vomiting. It was reported that she wrote a note to a nurse of whom she was fond and whom she called mother, which showed "sexual precocity" (we were never able to learn the exact content of the note).

After her return home things went on much as before. The vomiting and disinclination to take food remained about the same, with brief episodes of slight improvement. At one time the vomiting practically stopped when the younger sister spent a week with the grandmother. A great deal of stress was placed on the vomiting. The mother gave the child frequent fight talks in which she told her that she could stop if she would only try. Mealtimes became conversational sprints in the family's efforts to get the child's mind off the food. The telephone buzzed with anxious relatives calling to see if Helene had vomited that day. The mother, always irritable, became worse. The vomiting made her "furious." She would throw things at the child, threaten to choke her or to send her away to some place "where they will make you eat." Vomiting began to occur whenever any pressures were exerted on the child to make her do anything she did not want to do. The desire to have the mother wait on her increased. In the early part of the fall she was sent to school, but she refused to go after a few days because she was afraid she might vomit in school. Only with the greatest effort could she be induced to go out to play. Most of the time she lay around the house with her knees drawn up to her chin. Her posture was always slumped and her attitude one of dejection and unhappiness. Occasionally she would liven up enough to play cards with the family. At no time was there any complaint of headache, visual disturbance or difficulties in gait.

The history revealed much of note in the past and in the family setup. The child's birth and early development were not unusual except for a tendency to vomit in the first year. She was never breast fed. When she was 18 months of age celiac disease developed, for which she was treated until the age of 4 years, when she was placed on a normal diet. She was ill with this disease, vomiting frequently and weighing only 14 pounds (6.3 Kg.), according to the mother, at the age of 2 years. She received five transfusions, the mother acting as a donor for all. During this prolonged illness the parents were oversolicitous and pampering but nowhere near as concerned as during the later illness. The hospital bills were so large that the mother had to go to work and the child was cared for by the grandmother. In the meantime two abortions were performed on the mother before the family felt that they were justified in having another child.

At the age of 6 years Helene started to school, and the family moved away from the maternal grandmother. Although the child got B's the mother thought that she should do better ("That's only passing you know") and helped her with her homework so that she might get A's. Piano lessons were also begun when she was 6 years old. The mother, a pianist of sorts herself, always sat with Helene to practice. From the beginning she was cross and irritable with the child over these practice sessions, which usually ended with both of them in tears. The yelling and squabbling were so pronounced that the father when he came home from work would tell them to give up either the practicing or the quarreling. After the onset of the vomiting it would occur at these times too. Piano practice had been discontinued early in the summer before we saw Helene. In addition, the child was pushed with elocution and dancing lessons. It was difficult to see why she had not begun to vomit or to show symptoms of rebellion long before the onset of her difficulties, at 8 years. The mother was sure, however, that

there had been no change in her own attitudes immediately preceding the illness and that her severe punishing and her irritable manner had been present all along.

The mother had always been irritable and quick tempered, like her father. She had bitten her finger nails all of her life. She was emotionally overdependent on her own mother. She had been happily married to her husband for ten years. He had many business worries. A year or two before, he had suffered from "nervous belching and vomiting" for a short period. He was said to be easy-going in the home. The younger sister had rolled her head in the half-waking, half-sleeping state since she was 6 months of age.

The child was seen, in all, four times. Hospitalization was urged at the second visit but was repeatedly postponed by the mother, who was toying with the idea of turning Christian Scientist. The child was thin and emaciated. She sat slumped over with her knees about her chin. She appeared depressed and dejected. She talked in a low monotone, and her face was lit occasionally by a rather sickly grin. It the last two interviews she was more cheerful and looked up rather than at the floor. Her voice, too, became less expressionless. She spoke freely of her vomiting, which she regarded as a habit which she must stop herself. It was always preceded by nausea. "It comes up easy, I don't have to gag." It never occurred before breakfast. It was not "nice." When she vomited, she said, "my mother comes in and talks and sometimes hits me. She doesn't like me to do it. My father is disappointed." She felt that her appetite was improving. She did not want to go out to play or go to school because she might vomit. The only thing she recalled of her previous celiac disease was that she vomited.

Despite her mournful facial expression she maintained that she was happy. At times, however, she felt sad "like when people died," or as she might feel when "people die." She reported one dream of finding a lot of money behind a garbage can on the way home from school. She told with a great deal of pleasure of a story which she had read and liked because it was "nice." "They get locked up in a stork and it's all dark in there. There are babies and they had to tell stories to keep the babies from crying."

At first she spoke of her relations with her mother reluctantly, but later she became explicit in telling of the threats and scoldings. Her mother got mad at every one at home. She insisted that her mother loved her just the same even if she did get mad. "She says she loves me and I say she doesn't. She doesn't do things and that's what I like." She told her mother this in order that she might in that way make her do things for her. At times she wanted her mother to feed her, dress her and even to carry her about. "I want to try it out. I call her a dope and a lot of things." Helene insisted that she herself never got mad except once at the maid. "I never get mad, only cross." She admitted getting cross only with her sister, "because she does things I don't like." She felt that her sister got more breaks around the house than she did.

Psychologic tests were done Oct. 19, 1936. She cooperated well. Her reaction time was rapid, and at times she was careless. On the Stanford-Binet test she scored 9 years, 11 months (intelligence quotient 114). She showed a capacity for abstract reasoning. She did better on tests involving language material than on those depending on sensory impressions. On the Arthur scale she scored 7 years, 1 month (intelligence quotient 81). It was felt that her difficulty was partly the result of emotional factors. She seemed to feel less adequate in problems involving the perception of form. She persisted in her errors and worked in rather a frenzied fashion, trying impossible placements. Her greatest difficulty was on the Porteus mazes; her best work, on the Seguin form board. On the Goodenough drawing scale she scored 8 years. She concentrated on the

fingers and thumb and omitted clothing entirely. The total effect was rather weird. The Rorschach responses suggested a neurotic personality with some compulsive tendencies. A tendency to withdraw in the face of difficult situations was also suggested. There was nothing that suggested organic disease of the central nervous system to the interpreter.

Hiccups coming on in bouts were first reported October 22. Headaches first occurred on October 30. As the headaches increased the vomiting became less of a problem. During the last interview, on November 2, she was noted to yawn frequently. It was afterward reported that on that day she fell on the way home, and an unsteady gait was beginning to become apparent. On November 5 she complained of blurred vision, which persisted. Her gait at the same time became definitely ataxic. On November 6 she fell; the next day she was seen by an ophthalmologist, who noted a blurred left disk. These events were reported by the mother in a telephone call on November 8; she agreed to bring the child into the hospital. She now believed that the possibility of a tumor, which had been brought up before, deserved more serious consideration.

Helene was admitted to the Babies Hospital November 9 and transferred to the Neurological Institute a few hours later. Her physical signs were unmistakably those of a cerebellar neoplasm. Roentgen examination of the skull revealed nothing abnormal. On November 12, operation by Dr. C. A. Elsberg disclosed a midline cerebellar medulloblastoma. The child died several hours after the operation.

CASE 2.—Stanley W., a Jewish boy of 10 years, 3 months, was first seen on Jan. 18, 1937. He had been referred for psychiatric care from Vanderbilt Clinic, where an extensive pediatric work-up had shown no cause for his complaints. He had been brought by his parents at the request of his teacher, because of recent falling off in the quality of his school work. It was difficult to obtain an adequate history because of the vagueness of the parents, inconsistencies in their stories and language difficulties. A careful analysis of the data obtained from the parents, two of the sisters, the school and a hospital which they mentioned at that time gave us the following story.

The boy had always been "weak" and had presented feeding difficulties after an illness at 8 years of age. In April 1934, ten days after a tonsillectomy, he had been admitted to the Kingston Avenue Hospital, Brooklyn, with an attack of headache and vomiting with signs of meningeal irritation. The spinal fluid showed 2,340 cells but was sterile. He was discharged with a diagnosis of aseptic meningitis, a normal fluid and no abnormal physical findings. He was well except for the feeding difficulty and occasional vomiting until March 1936, when both of these symptoms became exaggerated. He began to have headaches and became "dopey." He lost weight rapidly and became so weak that he had to be carried about. The drowsiness and headaches gradually cleared and disappeared about September 1936. During the summer he had a "nervous cough." In June 1936 he was taken to the "Body and Soul Clinic," where he was treated with sedatives and hypnotism until September. During the summer he gained 15 pounds (6.75 Kg.) and slept up to fourteen hours a night. After his visits to the "clinic" he acted as if he were doped. When daily doses of phenobarbital (dosage not known) were discontinued, he began to make motions of tapping his forehead and his face. An eye-blinking tic also appeared.

The feeding problem was serious, meals taking up to an hour and a half. The family could get nowhere with threats, coaxing or punishment. At times he was forced to eat. Vomiting was not conspicuous. His school work fell off; although

his oral work remained fairly good, he could not finish his written work unless given a long time. He would become tired and lay his head on the desk. In contrast to his previous interest in school, he now did not seem to care. The father regarded this as laziness and would sit over him at night to make him study. On three or four occasions Stanley played hooky from school; he was unable to give a satisfactory reason for so doing. He became more boisterous and noisy in his behavior. This aggravated his parents, who found him increasingly more difficult to manage. He began to act silly and to clown. One of his sisters said, "He talks loud and laughs at things that are not funny. He copies slang expressions and darky dialect. Before he was a perfect gentleman—too quiet." Previously, he is said to have talked "like a 15 year old."

On the second visit the mother reported that he was eating better since she had reduced pressure on food intake. He had even begun to ask for food. She also said, "He ate till now because I want, now because he want."

Stanley was the only boy and the fourth of five children. His birth and early development were normal. He was breast fed until he was 18 months of age and received a bottle at night until he was 3 years old. Although physically small and never robust, he had been well up to the onset of his present troubles. The mother reported that he had some difficulty with one eye which a physician had said was congenital. She felt that he needed glasses but preferred to postpone ocular examination until after he was over his nervousness. When Stanley was born his parents and three older sisters were delighted. He was spoiled and catered to by all of the family. The father had never been as strict with him as with the girls. He had never actively associated with boys in their games, preferring to sit on the sidelines and watch their games. He had always been regarded as weak and delicate. The father at one time had hired another boy to carry Stanley's books. He had always been concerned about the boy's small size and "weak bones." He was given grade A milk whereas the rest of the family had to put up with grade B. The father felt that he could not punish Stanley until he became stronger. Friction had developed with a sister two years younger, who was already taller than the patient.

The parents, poorly educated Hungarian immigrants, were both irritable and could not stand noise. The father, an excitable, talkative man, was preoccupied with his failure as the family breadwinner following the loss of his business ten years before. He glossed over his reported happiness at the birth of a son and stressed only the way in which the boy took advantage of them at home. He was not an affectionate man but had always been closer to his daughters than to Stanley. In his contacts at the clinic he tended to talk himself up and to try to impress one with his abilities and what he might have been if he had had the opportunity. The mother was a rather phlegmatic person who did not reveal much of herself in interviews. She was observed to have rather a slow reaction time but seemed more understanding of the boy than did the father. One of the patient's sisters reported that he had an "uncanny understanding." She had begun to work three weeks after a meningitis episode and had observed that the patient was glad to see her stop work. The 15 year old sister who took care of the patient while the mother was at work was moderately mentally retarded and in a special class at school. The other siblings were normal and seemed to have made good adjustments.

Stanley was alert, spontaneous and polite during the interviews. He was restless, rarely sitting, and wandering about the room as he conversed. He talked in a loud voice and gesticulated frequently. From time to time he passed his hand over his forehead in a quick, ticlike manner. The frequency of this seemed to

have little bearing on the content of the interview at the moment. At times he was cautious, saying that his father knew more about that than he. If he were pushed at such times he became irritated. There was a tendency to indulge in puns and to accompany these with loud laughter. The following quotations serve to illustrate this tendency. While discussing his father's occupation he said, "A cloak presser. I don't know if it is a clock or a cloak." Again in relation to his father, "I sometimes call him pop. He says why not call him soda." While discussing his tendency to forget things he came over to me, poked me several times, clapped his hands, laughed, and said, "I'm telling you, if I was George Washington I'd be in a terrible hole. I'd forget it was war and everything."

He complained of occasional frontal headaches, occurring about once a month. There had been no dizziness since that associated with the posthypnotic state. He complained of difficulty in seeing with his left eye. He came to the clinic because of his "motions." He did not know the cause of these; they were not associated with headache. He did not believe that they were associated with his hypnotic experiences, during which there had been some manipulation of the forehead. He said that he nagged at his parents for ice cream or candy. Both parents punished him for this. He did not get hungry; this had begun when he was 2 or 3 years old. He regarded himself as being essentially a happy boy and did not take any of his difficulties seriously.

His discussions of his familial relations were full of wisecracks and digressions. He wished that his father could get a steady job so that his mother could be at home. "Sometimes my mother loves me better than my sisters. Sometimes she hates me because I nag and I cry I want candy or ice cream or soda." He gets along well with his father "except when he hits me." He resented the younger sister's being a head taller but stated that she did not know as much as he did. He fought with her a great deal; "When I fight I get on top of her and mobilize her. What does that mean?" On one occasion he stormed against all of his sisters, saying what pigs they were and what dirty language they used.

He told of "moping around" a lot. At these times he thinks back to "when I was a baby and my father bought me a bicycle. It's nice." He daydreamed at home and at school, where he got into trouble for losing his place. Aside from stating that he wanted to be a dentist when he grew up, and that he sometimes had daydreams of his career as a tooth puller when he might have to stand on the patient's stomach in order to do the extraction, he did not bring out any more of his fantasies.

Psychologic studies were done Jan. 28, 1937. During the tests it was observed that his emotional reactions were out of proportion to the situation. He was restless and wandered about the room investigating everything. He could not give sustained attention. His performance of the tests was consistent, and there was no wide scatter. On the Stanford-Binet test he scored 10 years, 9 months (intelligence quotient 105). He did least well on tests needing sustained attention. He was also given the Pintner-Paterson performance scale and scored 8 years, 6 months. There were no scores above the 10 year level, and he dropped to the 6 year level on the test with the Knox cubes. He worked without planning and impulsively plunged in with a trial and error method. On the Goodenough drawing scale he rated 8 years, 0 months. He drew a man with a huge body and a small head. The results of all of the tests were interpreted as showing a marked lack of emotional stability.

Stanley was seen four times; on his second visit arrangements were made to have him seen in the ophthalmic clinic. After this the parents no longer accompanied

him but sent him with a neighbor who knew little of the history. Ophthalmologic examination revealed a marked diminution of visual acuity without there being any refractive error. Visual acuity was 20/200 on the right and 20/70 on the left. He broke several subsequent appointments for the ophthalmic clinic, but he was finally seen again and roentgenograms of the skull were taken. Neurologic consultants concurred in the diagnosis of probable craniopharyngioma.

When the parents were seen to acquaint them with the findings, the father said, "Now we can tell it to you," and the reasons for some of their vagueness became apparent. He told of having taken Stanley to two other hospitals in June and August 1936 because of visual difficulties. "He was almost blind in one eye." At both hospitals the same diagnosis had been given them but they had refused to permit the child's admission. Subsequent letters from both hospitals reported that the boy had had a marked diminution in visual acuity on the left and similar roentgenolgoic findings. The family indicated that they had desired to find out how smart the doctors at the Medical Center really were. However, it seemed as if there were more than this to their unwillingness to face the problem and to their willingness to attribute all of the difficulties to "nervousness."

Stanley was admitted to the Babies Hospital on March 19, 1937. Examination revealed a chronic sinusitis. The left optic disk was thought to be normal by some observers and blurred by others. The right showed definite blurring. Neurologic examination by Dr. Walter Klingman gave normal results. Roentgen examination of the skull showed an increase in the size of the sella with intrasellar calcification. The visual fields showed bitemporal loss with some nasal encroachment. There was a delayed skeletal development. The dextrose tolerance curve was flat. The serum cholesterol content was 311 mg. per hundred cubic centimeters.

The child was transferred to the Neurological Institute on April 5. At operation by Dr. J. E. Scarff, on April 23, a large suprasellar cyst was found and drained of chocolate-colored fluid through a transcortical incision. A permanent opening was established between the roof of the cyst and the floor of the left lateral ventricle. He was discharged May 11, after a satisfactory postoperative course. He did well for a six week stay in a convalescent home but then lost some weight. The parents were both working, and his diet was insufficient. There was a recurrence of his pressure symptoms, on account of which he was readmitted for revision of the operation on July 20, 1938. Since then he has attended school and has been well. In the next year he gained 30 pounds (13.5 Kg.). The clowning and noisy behavior cleared up. The parents and the boy had no complaints when he was last seen, in September 1940. He was doing well at school in grade 8 B.

CASE 3.—Loretta D., a 10½ year old Jewish girl, the youngest of five children, was first seen March 25, 1940. She had been referred from the pediatric division of Vanderbilt Clinic, where her parents had taken her because of a feeding problem. Physical and laboratory examinations had revealed nothing unusual.

About three and a half years before, the child had begun to refuse to eat. Up to that time she had always been well, and one physician had even suggested a reducing diet, as she was overweight. The mother's emotional involvement in the feeding difficulties made the history somewhat hard to obtain. It would seem that at the end of the June term in 1936 the patient was skipped from grade 1 B to 2 B. She had been a good student. On the return to school in the fall the feeding difficulties began. At the end of that term she was placed in a "3" class because of a foreign accent. Loretta resented being separated

from her friends and began to dislike going to school. The lack of interest became more marked, and she lost weight. About March 1939 she began to vomit in the mornings on arising. There had been a slight amount of vomiting at the onset of the feeding disturbance, but this had quickly cleared up. In June 1939 the child was sent to a convalescent home for orthopedic patients cases because of the feeding problem and a slight scoliosis. She remained there for eight months, until February 1940. While there she did not gain in weight and the feeding problem remained unchanged. Vomiting was not conspicuous save for a four day period at the beginning when she was kept on a hyperextension frame. In spite of many varied approaches to the feeding difficulty, she did not eat. Otherwise, she made an exemplary adjustment, cooperating well in routines and getting along well with the other children in the play activities. In her school work she was inclined to be slow and needed urging. For the first ten days after her return home the mother reported that she ate well. Loretta reported that while at the convalescent home she began to get dizzy whenever her head was tipped backward. This had first occurred while she was on the frame. It could be brought out in the clinic by tilting her head back. She would become pale and stagger. However, if the change in position was produced slowly she did not seem to show such a marked reaction.

The vomiting became marked after her return home. Each morning she would waken at 5 or 6 o'clock and vomit. The parents would hold her head, rush frantically around for basins and exhort her to hold on. In the few weeks immediately before she was seen she occasionally complained of headache at this time. The feeding difficulty was especially exasperating to the whole family, who had always joined in attempts to get the child to eat. The parents were both sure that unless she ate she would be dead inside of a week. They threatened and even whipped her with a strap. The mother called her names, scolded and screamed. They starved her for a day or two at a time, with no change. The mother attempted to get the child to eat by going on a hunger strike herself. They tried to bribe her with promises of a college education and of new clothing. The mother said, "I say, 'you eat, I get you a new coat.' She say, 'so I do without.'" Holding her and forcing food in her mouth as well as an attempt to "cure" her with a dose of castor oil resulted only in the child's "almost fainting." The mother's introductory statement of the problem well expresses the handling. "I curse, I holler, I want to kill her. She won't chew. She takes an hour to eat." In addition to refusing to eat, the child would chew each mouthful a long time and claim that she could not swallow. During the prolonged chewing she would hold her head in her hands and act as if in a trance. If spoken to she told the family not to bother her.

Since the return from the convalescent home the child had become more demanding; she wanted to be waited on hand and foot. This tendency had been present in a milder form earlier in the illness. All members of the family willingly gave this service except the 13 year old sister, with whom Loretta had frequent squabbles. She grew restless and irritable and chewed at the cuticle of her finger and toe nails. Although there were no marked temper outbursts, she was apt to talk back to her mother if she was scolded, and tell her things that "hurt" her.

For the greater part of her illness the child had "dragged around" and acted tired and listless. She rarely had friends in, and had to be urged to go out to play. She was in grade 6A at school, and the quality of her work had not fallen off. In general, she had been quiet and easily managed and, according to a sister, "too good."

Her birth was normal and at term. The pregnancy was unwanted, and the mother took drugs in an attempt to abort. The mother particularly did not want a girl, as she had had three already. Loretta was breast fed for four months and then kept on a bottle until she started kindergarten, at the age of 4½ years. Her early development was not unusual.

The mother was a highly emotional Austrian Jewess, who cried frequently and who expected the child to eat all of everything she had prepared. She resented her inability to control the patient and said that before the onset of the feeding problem, "I could always deal with her the way I wanted." She seemed of limited intelligence, and it was difficult to get ideas across to her. The father, an irregularly employed cloak maker, was less emotionally involved in the problems than his wife but tended to back her up in her methods of dealing with the patient. He looked on the mother as "not very clever." He took a more responsible attitude toward the child's problems. The 17 year old sister seemed to have some insight into the home situation but felt that it would be difficult to go against her mother's decisions.

Loretta was seen five times in all. She was friendly but rather subdued. Although not particularly restless, she twisted her dress in her hands. She was never relaxed and never cheerful, although she would smile at infrequent intervals. It was difficult to get her to talk of anything but her symptoms, which she did in an old-womanish manner. "I never feel like eating; sometimes if my mother forces me, I vomit. When I try to eat it won't go down. I don't feel like eating." Thinking about food or smelling something which she did not like, she said "nauseates me." When she was eating she tried to think about something else, such as movies or stories she had read. She liked to be let alone while thinking of these things. She chewed her food a long time, even mashed potatoes, as she could not swallow. She did not believe that her food intake was particularly small. There were many foods which she disliked. At night she would sometimes dream of food and wake up nauseated. Occasionally, she would wake up early, and "I can't get anything to think about but food. It gets me naus-eous." For a short time she had been dizzy on awakening in the morning and if her mother forced her to drink fruit juices she would vomit. She could, however, eat grapefruit at these times without vomiting.

She became irritated at the other members of the family because of their mealtime behavior. "Sometimes I get sore but I don't say anything. It's inside but I wouldn't say anything bad." She became "disgusted" rather than angry. "I feel nauseous and she reminds me of it. I don't like to remember it. It's her fault if I get mad but I never say anything bad." Her father she believes "is fooling when he says I'll die. He's just trying to scare me so I'll eat." Every one at home hollered at her because of the eating except the sister she liked best and the brother. She enjoyed eating at a neighbor's house in relative peace and quiet, though her intake was no better.

Loretta did not feel that she was much good at anything. She could not play as well as her classmates; she could not draw well; nor was she good at school work, in particular, geography. She expressed fears of being alone in a room and of wanting a light on. "I think a man is there. He's bending over me and I think he's going to tie something over my mouth so I can't scream." She had frightening dreams about shooting and fighting. "I'm always the hero. I don't shoot any one but I get them just the same." She was easily frightened in the movies. These fears she dated to two years before, when she "caught" them from a playmate who "always got frightened."

Psychologic tests were done on April 4, 1940. She was less responsive and less stimulated by the tests than most children. Her opinions and responses were definite. She was slow in movements and underproductive in creative situations. No abnormalities in form perception were noted. On the Stanford-Binet test she scored 14 years, 5 months (intelligence quotient 137). Rote memory and memory for ideas were good. A weakness in tests involving social judgment was noted. The Arthur score was 10 years, 8 months (intelligence quotient 101). Work on tests involving spatial form was slow but showed good analysis. With the Kohs blocks she scored 10 years. On the Goodenough drawing scale she rated 11 years, 6 months. She drew a well proportioned figure with adequate detail. The Rorschach responses were few; she saw nothing on seven of the ten cards. Her responses were said to suggest anxiety.

From the beginning it has been apparent that the situation was unusual. The child had shown no improvement in an emotionally neutral environment away from home. This is unusual in most of the emotionally determined feeding disorders of childhood. The symptoms had suggested intracranial tumor, but there had been no findings to back this up. At the time of the last visit the child complained of increasing dizziness not associated with changes in the position of the head, and of increasingly severe "banging" headaches. On the way to the clinic that day she had had a peculiar attack of numbness in the left hand lasting twenty minutes. The hand was examined as the numbness was leaving. There was a glove distribution of hyperesthesia, which disappeared in about ten minutes.

Because of the increase in symptoms she was admitted to the Babies Hospital on that day, April 30, 1940, for observation for tumor of the brain. Physical examination revealed nothing unusual. Neurologic examination by Dr. Walter O. Klingman showed a slight unsteadiness in the gait, which was tested shortly after a dizzy spell. The reflexes were all hyperactive, with ankle clonus bilaterally. Nonequilibratory tests gave normal results. No nystagmus was observed. Roentgen examination of the skull revealed nothing abnormal. An electroencephalogram showed a "posterior focus." The results of vestibular tests were normal. An ophthalmologic consultant thought that the optic disks were normal. Vomiting was not conspicuous during her stay here or later at the Neurological Institute, where she was transferred on May 6, because of the clinical suspicion and the electroencephalographic findings. Gradually slight ataxia, nystagmus and an early papilledema developed. It was felt that she had a cerebellar tumor. At operation on May 20, by Dr. J. E. Scarff, an ependymoma arising from the floor of the fourth ventricle and filling it was found and partially removed. Convalescence was smooth. She has had two courses of radiotherapy.

During the summer she spent a period in the country with her mother and gained 10 pounds (4.5 Kg.). The mother at present has the same complaints of poor appetite as before and talks in the same way of her attempts to get the child to eat. The child, however, does not vomit or go into trances at the table. There is no difficulty in swallowing. The patient states that her mother does not press her to eat as she did before. "If I don't want to eat I don't have to." Her father backs her up.

COMMENT

All 3 of these children presented behavior disorders of a type frequently seen in the practice of pediatrics or child psychiatry. All had a feeding disorder which was handled unwisely by the parents. In cases 1 and 3 the disturbance in appetite was the first symptom noted

and did not improve during periods of one and eight months away from the home. The anorexia seems most probably to have been primarily of central origin. Both children had a tumor of the posterior fossa. In case 3 there was a transitory improvement in the appetite on the child's return from the convalescent home, and in case 1 the vomiting cleared up almost completely when the sister of the patient, of whom she had become jealous, went away on a visit. In case 2 the feeding problem began after an illness and lasted for three years. The onset was at a time when the mother had gone out to work and the boy was left largely in the care of a mentally retarded older sister. His appetite improved during a period when his parents were able to ease up in their methods of handling the feeding situation. The feeding problem had been more troublesome some months before the boy was seen, at a time when headache, vomiting and visual disturbances were extreme. One is justified in believing that the intracranial pressure was increased at that time and subsequently decreased. One cannot entirely rule out central factors as a cause of the anorexia in this patient, but the emotional factors seem to be more prominent than in the other two patients.

There are other similarities. In cases 1 and 3 and to a lesser extent in case 2 there developed early in the course of the illness a regressive type of personality change, with a desire to be babied and waited on, resentment of attention given other children in the home and a growing jealousy not present before, and listlessness and withdrawal of interest from normal occupations. Two patients had fantasies having to do with satisfying infantile experiences; the third indulged in daydreams to get away from the thought of food. This is not an unusual type of personality reaction in children who find themselves confronted with anxiety-provoking and difficult situations. Many children with an acute illness of any sort become babyish and demand attention and want to be waited on. Anxiety and emotional insecurity were indicated in all 3 of the children. The 2 girls with tumors of the posterior fossa were repressed, displayed motor restlessness and bit their finger nails. This behavior is not peculiar to children with tumors of the brain. The boy with the craniopharyngioma showed emotional instability, and noisy, boisterous, hyperactive behavior with a tendency to clown and annoy his family with wisecracks which were not always funny. He had difficulty in fixing his attention and complained of memory disturbances. These symptoms have been described as accompanying frontal lobe tumors in adults but are common in children in whom there is no evidence of organic disease of the central nervous system.

In persons with intracranial neoplasms symptoms which cannot be attributed to the location are often said to be due to a generalized increase in intracranial pressure. In none of our children was there any good evidence for this being the case; in the first child a lumbar tap was done at a time when the personality disorder was well marked and

the spinal fluid pressure was found to be normal. There was no drowsiness, confusion or mental dulness. The patients were all alert and did well on psychometric examination. It would be stretching a point to attribute the majority of the personality and behavior symptoms in these children to local cerebral damage or to a generalized increase in intracranial pressure.

Emotional factors loom large in all of our patients. The way in which they utilized their symptoms and in which they reacted to their milieu is evident. The fact remains that they all had intracranial tumors. How best can one view these personality disorders? What part of the picture is due directly to the tumor or to changes in intracranial pressure, and what to secondarily arising emotional disorders? Neither Roback nor Keschner and his associates in the cases previously cited were able to evaluate the relation of the emotional factors to the tumors of the brain.

Although there is little in the literature about the personality changes in children with tumors of the brain, a great deal has been written about the disturbances seen in adults. A brief survey would seem to be of help in understanding the personality disorders observed in our patients. There is an increasing tendency to look on many of the mental symptoms associated with intracranial neoplasms as part of more or less general disorders of personality rather than as aids in localization of the tumors. The symptom *Witzelsucht,* a tendency to clowning and waggishness (observed in case 2), commonly associated with damage to the frontal lobe, has been held by many observers to occur relatively infrequently, even with tumors of the frontal lobe and to be present with those of other sites. It seems to depend more on the previous personality than on specific damage to the frontal lobe, according to Golla,[7] who defined it as a defense mechanism. Kinnier Wilson [7] said in 1931 that "every neurologist of experience must now agree that the localizing value of mental symptoms in cases of cerebral tumor is practically nil." Minski [8] and others have pointed out that the mental symptoms depend more on the rate of growth of a tumor and the previous personality of the patient than on the localization. With slow-growing tumors personality changes are said to predominate; with rapidly growing tumors only slight personality changes are observed but marked changes in the intellectual sphere, especially clouding of consciousness, are apt to occur. The drowsiness, apathy, stupor and confusion seen with generalized increase of intracranial pressure, which clear up with decompression or after the use of hypertonic solutions, are commonly seen in the end stages of tumor in children, but they are quite different from the personality changes observed in our patients. Gordon Holmes [7] noted

7. Holmes, G., and others: Discussion on the Mental Symptoms Associated with Brain Tumors, Proc. Roy. Soc. Med. **24**:997-1008 (May) 1931.

8. Minski, L.: The Mental Symptoms Associated with Fifty-Eight Cases of Cerebral Tumor, J. Neurol. & Psychopath. **13**:330-343 (April) 1933.

that paralyses, visual disturbances, vomiting, headaches and convulsive attacks often evoke emotionally determined reactions of anxiety or depression. He also observed that disturbances in speech caused by focal damage often led to irritability, excitement or depression. Kanzer [9] pointed out that such reactions if seen in a case of pulmonary disease would be regarded as emotional disorders but that they are often looked on as the specific result of damage to a particular area of the brain if the presence of a cerebral neoplasm was ascertained. In discussing the psychopathology of tumors of the brain in adults he noted that there is a constant striving in the behavior of the patient to adjust to his problems and to cling to the habitual course of his former life. The existence of a pathologic mental state, in his opinion, is usually unsuspected until after the occurrence of some dramatic episode or the development of a situation in which some special demand is made on the patient's capacities. Such a demand may often be occupationally determined. The patient's adaptive resources are marshaled to cope with the increasing disability and to maintain normal life. Irritability, restlessness, facetiousness and confabulations occur as more or less active attempts to surmount his deficiencies. Anxiety and depression are also aroused. As the disability becomes more marked and the capacity for active adjustment is exceeded, indifference, apathy, lack of concentration and cooperation, loss of insight, and euphoria are seen as the patient develops an attitude of refusing to recognize or deny his illness. These various defense reactions are essentially similar to those found in the common psychoneuroses, and their function in protecting a person against psychically overwhelming situations is identical. He believes that the nature of the secondary emotional reactions to aphasias, agnosias, apraxias and hallucinations, which may have some localizing value, are largely determined by the premorbid personality and the previous life history. General symptoms such as "poor memory" if carefully analyzed may show an aphasic word-finding difficulty. Minski [8] in a psychiatric study of 58 cases of tumor of the brain found that the relatives of the patients associated the onset of mental symptoms with physical or mental stress. He reasoned that the presence of an organic lesion must make the patient's adaptability to any additional worry or stress less than normal because of the interference with the function of the brain as an integrated whole. When he has to face undue stress the patient is unable to cope with it and reacts with emotionally determined symptoms. The patient with a tumor of the brain may utilize his symptoms to gain attention and achieve emotional ends just as may a person with any other illness. This tendency is common in all illnesses in childhood. Kanzer wondered if the relative paucity of mental symptoms in children with tumors of the brain is not partly

9. Kanzer, M.: Personality Disorders with Brain Tumors, Am. J. Psychiat. **97**:812-830 (Jan.) 1941.

a result of the less rigid social criticism to which they are subjected. Certainly in our 3 cases the children were subjected to many unreasonable environmental demands and pressures.

With these points of view in mind, it becomes a little easier to try to understand what is going on in our patients. In our first case, the child had apparently been able to get along reasonably well in spite of the attitudes of a tense, irritable, hostile mother. The anorexia and later the vomiting intensified the unreasonable attitudes in the parent. The regressive personality symptoms, however, appeared before the vomiting was manifest. It seems most likely that the presence of the tumor interfered with the normal functioning of the brain as an integrated whole and the child was no longer able to cope with the situational stress. She reacted with an emotionally determined disorder of the whole personality. Through her wish to be babied she was able to force the mother to give her the care and attention which were concrete evidence that she was loved. She resented attentions being given to her sister. She expressed her resentment and hostility through vomiting, a common method of children who are unable to express hostility openly. She, it will be remembered, was unable to get mad at any one except the maid, and that only once. It is of interest that the vomiting nearly completely stopped when the sister was away and the patient had the undivided attention of the mother. The way in which the child used the vomiting to achieve emotional ends is of interest especially because it seems fairly certain that the symptom was primarily of central origin, resulting from pressure on the bulb. Depression and increasing anxiety and tension came on as the tumor symptoms increased and the parental "furiousness" became more marked.

In the third case, that of a girl with an ependymoma arising from the floor of the fourth ventricle, the situation is a little different. The anorexia was again of central origin, but, although the child was unwanted, the emotionally traumatic behavior of the mother was not particularly in evidence until after the appearance of the appetite disturbance. The personality disorder cleared up during the patient's eight months' stay in a convalescent home, although the anorexia continued, only to recur with the return of the child to the home setting. The personality and behavior difficulties all seem to be related to the anorexia and the methods which the whole family, led by the mother, used to get the child to eat. Again we deal with a child who could not adequately express anger and resentment toward the parents and who could not shoot even in her dreams. She got "sore" inside but never said anything bad. Characteristically, she came to have a regressive, withdrawing type of emotional disorder associated with anxiety, inferiority feelings and mild fears. In view of the child's general personality, an aggressive, rebellious type of behavior disorder could not have occurred.

In the remaining case, the development of the personality disorder cannot be so simply and easily explained. There were certain mental symptoms which were probably due to the compression of the frontal lobes by the large suprasellar cyst. The boy was unable to fixate his attention for more than a brief period; he complained of memory difficulties, and at school his teacher noted that although his oral work remained good he could not finish his written work. It is possible that some specific language dysfunction was operating. There was diminution in vision, and he tired easily. In spite of these symptoms he continued at school, and the quality of his work fell off. Although the attitude at school was sympathetic, the father regarded him as lazy and lacking in ambition and sat over him with an iron hand as he did his homework. In addition, there were the unreasonable methods of handling the feeding disturbance. The boy had previously been pampered and spoiled by the parents and the four sisters; the father, especially, had been worried about his small size. The father had grown increasingly annoyed and critical of the boy's behavior and had become less protective in many ways. The role of the hypnotic experiences and of the parents' refusal to accept the previously given correct diagnosis is not clear from the information available, but it seems likely that they must have played a part in the patient's reactions. The boy did resent the sister's being taller than himself. The more general personality and behavior symptoms which developed in the boy seem to have arisen as emotional reactions to the specific symptoms due to the suprasellar cyst and also as reactions to the unreasonable pressures and criticisms at home. They fall into two groups. The first, and least severe group, consists of mild withdrawal and daydreaming about infantile satisfactions with mildly aggressive tooth pulling. The other symptoms seem to serve more as defenses and active measures to cope with his deficiencies. He became hyperactive and boisterous. His clowning and waggishness in the interviews frequently served as a defense and as a way to cover up when pressures were put on him. Tics and irritability seemed related to anxiety produced in the boy by his deficiencies, caused directly by his tumor, and by the environmental pressures.

We realize that we are probably guilty of too much oversimplification in the foregoing attempt to evaluate and interpret the relative roles of organic and emotional factors in the genesis of the personality disorders of our patients. However, a more lengthy analysis would add little and might serve only to confuse. It becomes evident that the environmental pressures were of great importance in the devlopment of the difficulties for which the children were referred to the psychiatric clinic. Mental symptoms due to direct involvement of the brain itself seemed to be absent in the 2 cases of tumor of the posterior fossa and were only a part of the picture in the other case. The regressive, withdrawal type of personality reaction is not uncommon in physically ill children. In our

cases, however, it seems to have been more severe than that usually observed during illnesses, and in case 3 it was certainly related to the family pressures, as it cleared up when the patient was away from home. We should be inclined to agree with Kanzer that perhaps the reason for the infrequency of general personality disorders in children with tumors of the brain is at least in part related to the lack of rigid social criticism. The untoward environmental pressures and the emotional reactions they caused were a large part of the picture in our patients.

From the purely neurologic standpoint there were signs and symptoms, in retrospect, that were overshadowed by the emotional features. However, aside from the vomiting, the hiccup and yawning were suggestive of central disease. Likewise, in the third case the vertigo induced only by a change in position suggested very strongly a cerebellar or brain stem lesion. The postural attitudes in the cases of tumor of the posterior fossa may have had some significance, either in indicating a change in tonus of the cervical and spinal muscle groups or as protective attitudes for relief of mild irritative meningeal phenomena due to pressure.

Surprisingly, none of the patients showed any separation of the cranial sutures or erosion of the clinoid processes, sometimes seen in cases of long-standing increased intracranial pressure.

SUMMARY AND CONCLUSIONS

Mental symptoms in children with intracranial tumors have not been stressed in the literature.

The case histories of 3 children with intracranial neoplasms who presented behavior disorders and who were studied in a psychiatric clinic are detailed. Two children had tumors of the posterior fossa, and 1 had a craniopharyngioma.

An attempt is made to understand the personality disorders present in terms of the relative roles of the organic and emotional factors.

In the 2 cases of tumors of the posterior fossa it is suggested that the personality disorders observed were due to emotional reactions in the child to unreasonable and severely emotionally traumatic environmental pressures. In 1 case the pressures were related to the anorexia produced by the tumor, and in the other they had existed previously but the child had apparently been able to cope with an unfavorable milieu until the developing tumor interfered with the normally integrated behavior.

In the case of craniopharyngioma it is suggested that there were present some specific symptoms attributable to damage to the frontal lobes. The more general personality and behavior disorders seemed related to the child's efforts to overcome these deficiencies in the face of unfavorable environmental pressures.

The type of disorder observed depended more on the personality of the patient than on the location of the tumor.

It is suggested that the relative infrequency of mental and behavior symptoms in reported cases of children with tumors of the brain is due to the rapidity with which such tumors go on to produce definite signs of increased intracranial pressure and signs of local damage by the neoplasm, and to the relatively favorable milieu of most of the children, in contrast to the markedly unsatisfactory environments of our patients.

Further psychiatric studies of children with intracranial tumors would be of interest if they could be done without unnecessarily postponing operative intervention.

WHOOPING COUGH VACCINE

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ATLANTA, GA.

This report is a continuation of the work published in September 1936 [1] and describes a comprehensive study of seven different vaccines.

1. SAUER'S REGULAR VACCINE (10 BILLION COUNT)

The study of this vaccine was covered in the previous paper.

2. COMBINED DIPHTHERIA TOXOID AND PERTUSSIS VACCINE B-5325

This vaccine contained 20 billion pertussis organisms per cubic centimeter and 20 Lf units of diphtheria toxoid.

The vaccine was given in three doses at weekly intervals: 1 cc., 2 cc. and 2 cc. The local reactions were slightly greater than those produced by the regular 20 billion count vaccine. The systemic reactions were the same as with the 20 billion count vaccine.

All patients were given Schick tests one week before receiving the vaccine, and all those given this vaccine had positive reactions. Three months after the last injection of vaccine they were again given Schick tests, and at this time the reactions were negative. The diphtheria antitoxin titers ran between 3 and — 0.002. As will be noted, there was a marked variation.

Complement fixation tests were made one week after the last injection. The incidence of 4 plus reactions was not so high in this group as in the group receiving equal amounts of the regular 20 billion count pertussis vaccine; but on studying the work sheet it will be noted that there were a large number of 3 plus reactions. These patients received enough diphtheria toxoid to produce a negative Schick reaction, and with a slight increase in the pertussis count of pertussis organisms the 3 plus reactions could be changed to 4 plus. Therefore, this vaccine would give excellent results and the two immunizations could be carried on at once.

The clinic was conducted at the Central Presbyterian Clinic for Children.

Ethel Nolan, R. N., in charge of the clinic, collaborated in all clinical work.

Eli Lilly & Company furnished the vaccines and antigen used in the clinical work.

Complement fixation tests and titrations were done by the Lilly Research Laboratories.

1. Daughtry-Denmark, L.: Studies in Whooping Cough: Diagnosis and Immunization, Am. J. Dis. Child. **52**:587-598 (Sept.) 1936.

The data for individual patients are shown in the following tabulation:

Number	Name	Age	Schick Reaction	Cc.	Complement Fixation	Antitoxin Titer	Schick Reaction
1	B. R.	5 yr.	Pos.	5	++++	.....	Neg.
2	C. A.	8 mo.	Pos.	5	+++	.....	Neg.
3	R. C.	7 mo.	Pos.	5	−	.....	Neg.
4	N. C.	2½ yr.	Pos.	5	−	.....	Neg.
5	R. C.	7 mo.	Pos.	5	++++	.....	Neg.
6	J. F.	1 yr.	Pos.	5	++++	.....	Neg.
7	L. H.	7 mo.	Pos.	5	+	.....	Neg.
8	V. L.	1 yr.	Pos.	5	−	.....	Neg.
9	W. S.	3½ yr.	Pos.	5	−	.....	Neg.
10	J. B.	1 yr.	Pos.	5	+	.....	Neg.
11	M. B.	4 yr.	Pos.	5	++++	.....	Neg.
12	H. R.	3 yr.	Pos.	5	++	.....	Neg.
13	K. N.	11 mo.	Pos.	5	−	.....	Neg.
14	J. C.	6 mo.	Pos.	5	+++	.....	Neg.
15	J. M.	11 mo.	Pos.	5	+++	.....	Neg.
16	P. M.	11 mo.	Pos.	5	+++	.....	Neg.
17	M. M.	18 mo.	Pos.	5	++++	.....	Neg.
18	L. A.	10 mo.	Pos.	5	++	.....	Neg.
19	B. T.	1 yr.	Pos.	5	++++	.....	Neg.
20	M. D.	18 mo.	Pos.	5	−	.....	Neg.
21	B. W.	11 mo.	Pos.	5	+++	.....	Neg.
22	B. B.	11 mo.	Pos.	5	++++	.....	Neg.
23	J. M.	18 mo.	Pos.	5	++++	.....	Neg.
24	J. M.	2½ yr.	Pos.	5	++++	.....	Neg.
25	D. M.	6 mo.	Pos.	5	++++	.....	Neg.
26	T. M.	1½ yr.	Pos.	5	++++	.....	Neg.
27	T. O.	11 mo.	Pos.	5	+++	.....	Neg.
28	B. L.	10 mo.	Pos.	5	+++	.....	Neg.
29	E. B.	20 mo.	Pos.	5	++	.....	Neg.
30	M. D.	15 mo.	Pos.	5	++	.....	Neg.
31	P. T.	17 mo.	Pos.	5	++	.....	Neg.
32	P. H.	19 mo.	Pos.	5	++++	.....	Neg.
33	R. C.	6 mo.	Pos.	5	+++	.....	Neg.
34	S. P.	2½ yr.	Pos.	5	−	.....	Neg.
35	A. H.	4 yr.	Pos.	5	++	.....	Neg.
36	N. M.	3 yr.	Pos.	5	+	.....	Neg.
37	M. H.	1 yr.	Pos.	5	+	.....	Neg.
38	P. D.	1 yr.	Pos.	5	+	.....	Neg.
39	N. R.	8 mo.	Pos.	5	+	.....	Neg.
40	J. B.	6 mo.	Pos.	5	++	.....	Neg.
41	J. C.	10 mo.	Pos.	5	++++	.....	Neg.
42	B. L.	9 mo.	Pos.	5	+++	.....	Neg.
43	K. H.	8 mo.	Pos.	5	.....	.....	Neg.
44	B. P.	6 mo.	Pos.	5	++++	.....	Neg.
45	F. P.	5 yr.	Pos.	5	.....	.....	Neg.
46	W. A.	1 yr.	Pos.	5	++++	0.1	Neg.
47	B. M.	2 yr.	Pos.	5	++++	0.002	Neg.
48	W. D.	10 mo.	Pos.	5	+++	0.1	Neg.
49	C. R.	1 yr.	Pos.	5	.....	0.1	Neg.
50	W. C.	2 yr.	Pos.	5	++++	0.002	Neg.
51	H. B.	10 mo.	Pos.	5	++	−0.002	Neg.
52	O. B.	10 mo.	Pos.	5	++	−0.002	Neg.
53	F. I.	8 mo.	Pos.	5	++++	0.002	Neg.
54	H. R.	3½ yr.	Pos.	5	++++	0.01	Neg.
55	H. B.	13 mo.	Pos.	5	++	−0.002	Neg.
56	J. G.	4 yr.	Pos.	5	+++	−0.002	Neg.
57	A. S.	20 mo.	Pos.	5	++++	3.0	Neg.
58	R. P.	8 mo.	Pos.	5	+	−0.002	Neg.
59	E. L.	8 mo.	Pos.	5	++++	0.01	Neg.
60	B. E.	8 mo.	Pos.	5	+	0.002	Neg.
61	R. R.	6 mo.	Pos.	5	++++	0.01	Neg.
62	F. E.	9 mo.	Pos.	5	+++	−0.002	Neg.
63	J. H.	1 yr.	Pos.	5	+++	IQ	Neg.
64	P. M.	22 mo.	Pos.	5	+++	0.1	Neg.
65	H. S.	4 yr.	Pos.	5	+++	0.002	Neg.
66	D. T.	2 yr.	Pos.	5	+++	0.1	Neg.
67	B. H.	8 mo.	Pos.	5	+++	0.002	Neg.
68	F. E.	2½ yr.	Pos.	5	+++	IQ	Neg.
69	B. A.	14 mo.	Pos.	5	+++	0.1	Neg.
70	S. M.	6 mo.	Pos.	5	+++	−0.002	Neg.
71	J. E.	6 mo.	Pos.	5	+++	0.002	Neg.
72	G. H.	5 yr.	Pos.	5	++++	0.002	Neg.
73	P. H.	2 yr.	Pos.	5	+++	−0.002	Neg.
74	B. S.	14 mo.	Pos.	5	++++	0.002	Neg.
75	G. P.	1 yr.	Pos.	5	+++	0.1	Neg.
76	F. H.	7 mo.	Pos.	5	++++	0.002	Neg.
77	M. V.	11 mo.	Pos.	5	++++	0.01	Neg.

Number	Name	Age	Schick Reaction	Cc.	Complement Fixation	Antitoxin Titer	Schick Reaction
78	R. V.	2 yr.	Pos.	5	++++	0.1	Neg.
79	B. S.	5 yr.	Pos.	5	++	0.1	Neg.
80	G. M.	18 mo.	Pos.	5	++++	0.1	Neg.
81	R. H.	14 mo.	Pos.	5	++++	0.1	Neg.
82	B. M.	11 mo.	Pos.	5	+++	0.1	Neg.
83	S. C.	7 mo.	Pos.	5	+++	.....	Neg.
84	D. B.	7 mo.	Pos.	5	++++	0.002	Neg.

81 complement fixation tests
30 ++++—37%
74 + or better—91.3%
38 titrations
30 above —0.002—79%

3. PERTUSSIS VACCINE, ALUM PRECIPITATED, NO. 4817 B (20 BILLION COUNT)

This vaccine contains 20 billion pertussis organisms per cubic centimeter and was given in the following doses: 0.2 cc., 0.4 cc. and 0.4 cc., a total of 1 cc.

The local reaction was very similar to that produced by alum-precipitated diphtheria toxoid. Two abscesses developed. In an occasional child a hard area about 0.5 cm. in diameter could be palpated for three weeks after the injection.

The systemic reaction was the same as that produced by the regular pertussis vaccine—a slight fever for eight to ten hours.

Complement fixation tests were done one week after the last injection. These patients received a total of 20 billion pertussis organisms. The results were as follows:

Number	Name	Age	Amount, Cc.	Complement Fixation
1	A. C.	3 yr.	1	—
2	C. S.	18 mo.	1	+
3	R. S.	5 yr.	1	+
4	M. S.	3 yr.	1	+
5	M. C.	2½ yr.	1	+
6	M. J.	2 yr.	1	+++
7	B. C.	7 mo.	1	++++
8	M. A.	1 yr.	1	++++
9	J. B.	5 yr.	1	++++
10	S. G.	18 mo.	1	++++
11	J. G.	4 yr.	1	++
12	C. G.	4 yr.	1	++++
13	F. S.	3 yr.	1	+++
14	B. G.	15 mo.	1	++++
15	J. C.	4 yr.	1	++
16	F. S.	18 mo.	1	+++
17	C. T.	4½ yr.	1	++++
18	C. E.	2 yr.	1	++++
19	D. T.	10 mo.	1	++
20	G. K.	10 mo.	1	++
21	M. C.	4½ yr.	1	++++
22	S. W.	2 yr.	1	++
23	R. C.	3 yr.	1	++++
24	E. W.	9 mo.	1	++++
25	C. W.	5 yr.	1	++++
26	S. F.	2 yr.	1	—
27	S. B.	4 yr.	1	++++
28	J. S.	2 yr.	1	++
29	S. R.	2 yr.	1	++++
30	B. R.	23 mo.	1	++++
31	W. A.	2½ yr.	1	++++
32	J. M.	7 yr.	1	++
33	D. A.	17 mo.	1	++++

Number	Name	Age	Amount, Cc.	Complement Fixation
34	E. M.	3 yr.	1	++++
35	M. H.	7 mo.	1	−
36	F. J.	7 mo.	1	++++
37	A. J.	6 mo.	1	++++
38	M. J.	11 mo.	1	++
39	R. P.	6 mo.	1	++++
40	C. S.	3 yr.	1	++++
41	J. L.	3 yr.	1	++++
42	R. W.	2 yr.	1	++
43	M. A.	4 yr.	1	+
44	R. S.	8 mo.	1	++++
45	G. M.	15 mo.	1	++++
46	B. N.	2 yr.	1	++++
47	C. P.	3 yr.	1	++
48	H. H.	7 mo.	1	+++
49	R. S.	3 yr.	1	−
50	C. H.	2½ yr.	1	−
51	R. H.	9 mo.	1	++
52	M. M.	3 yr.	1	++
53	G. M.	7 yr.	1	−
54	C. D.	2½ yr.	1	−
55	D. C.	9 mo.	1	++++
56	W. D.	10 mo.	1	−
57	N. J.	11 mo.	1	−
58	D. J.	5 yr.	1	++
59	D. C.	9 mo.	1	++++
60	J. S.	9 mo.	1	++
61	J. M.	9 mo.	1	+
62	G. P.	8 mo.	1	++
63	H. J.	1½ yr.	1	−
64	J. B.	1 yr.	1	−
65	J. M.	2 yr.	1	+
66	G. T.	4 yr.	1	+
67	B. C.	1 yr.	1	−
68	M. M.	9 mo.	1	+
69	J. B.	3 yr.	1	−
70	B. H.	5 yr.	1	++++
71	P. R.	1 yr.	1	++
72	J. K.	6 yr.	1	++
73	D. W.	11 mo.	1	+
74	P. B.	7 yr.	1	−
75	P. J.	19 mo.	1	+
76	A. G.	19 mo.	1	++++
77	S. L.	18 mo.	1	++++
78	P. S.	16 mo.	1	++
79	P. A.	4 yr.	1	+
80	R. S.	11 mo.	1	++++
81	S. M.	5 yr.	1	++
82	W. C.	2 yr.	1	++
83	V. J.	6 yr.	1	+
84	J. B.	7 mo.	1	+
85	H. H.	6 mo.	1	+
86	E. T.	5½ yr.	1	++
87	R. C.	3½ yr.	1	−
88	C. S.	18 mo.	1	+
89	R. S.	5 yr.	1	+
90	B. L.	6 mo.	1	+
91	S. F.	13 mo.	1	++++
92	W. A.	4 yr.	1	+++
93	J. A.	2½ yr.	1	+
94	J. J.	4 yr.	1	++++
95	L. B.	1 yr.	1	++++
96	M. H.	1 yr.	1	+++
97	J. D.	2½ yr.	1	++++
98	E. Z.	1½ yr.	1	++++
99	C. M.	3 yr.	1	−
100	J. P.	6 yr.	1	++++
101	O. B.	9 mo.	1	++++
102	E. H.	4 yr.	1	++++
103	J. E.	3 yr.	1	++
104	P. Q.	2 yr.	1	++++

Number	Name	Age	Amount of Alum-Precipitated Toxoid Received Before Coming to Clinic, Cc.	Complement Fixation	Antitoxin Titer
1	J. G.	4 yr.	1	++	.....
2	C. G.	6 yr.	1	++++	.....
3	F. S.	3 yr.	1	++	.....
4	D. G.	15 mo.	1	++++	.....
5	J. C.	4 yr.	1	++	.....
6	C. F.	18 mo.	1	+	0.002
7	C. T.	4½ yr.	1	++++	0.002
8	C. E.	2½ yr.	1	+	0.002
9	J. K.	10 mo.	1	++	0.01
10	M. C.	4½ yr.	1	++++	0.002
11	S. W.	5½ yr.	1	+++	0.01
12	R. C.	3 yr.	1	++++	—0.002
13	E. W.	9 mo.	1	++++	—0.002
14	C. W.	5 yr.	1	++++	0.002
15	S. S.	2 yr.	1	—	0.002
16	S. E.	4 yr.	1	++++	0.1
17	J. S.	2 yr.	1	+	0.002
18	S. R.	2 yr.	1	++++	—0.002
19	B. R.	23 mo.	1	++++	—0.1
20	W. A.	2½ yr.	1	++++	0.002
21	J. M.	7 yr.	1	++	0.01
22	D. A.	17 mo.	1	++++	0.01
23	E. M.	3 yr.	1	++++	0.002
24	M. H.	7 mo.	1	—	0.002
25	F. J.	7 mo.	1	++++	—0.1
26	A. G.	6 mo.	1	++++	—0.002
27	M. T.	11 mo.	1	++	0.002
28	R. P.	16 mo.	1	++++	0.002
29	C. S.	3 yr.	1	++++	0.1
30	J. L.	3 yr.	1	++++	0.002
31	B. L.	6 mo.	1	+	0.002
32	S. F.	13 mo.	1	++++	0.002
33	W. A.	4 yr.	1	++++	.....
34	J. J.	4 yr.	1	++++	0.002
35	L. B.	1 yr.	1	++++	.....

139 patients
18 negative complement fixations—12.9%
63 ++++ complement fixations—45.3%
121 positive complement fixations—87.1%

4. PERTUSSIS VACCINE, ALUM PRECIPITATED, NO. 4817 A (40 BILLION COUNT)

This vaccine contained 40 billion pertussis organisms per cubic centimeter. The total dose was 1 cc. The vaccine was given at weekly intervals in the following doses: 0.2, 0.4 and 0.4 cc. Even though the vaccine was twice as concentrated as the alum-precipitated pertussis vaccine No. 4817 B, the local and systemic reactions were the same. The patients received a total of 40 billion organisms, with the following results:

Number	Name	Age	Amount, Cc.	Complement Fixation
1	B. B.	5 yr.	1	++++
2	J. S.	16 mo.	1	++++
3	G. M.	3 yr.	1	+++
4	C. S.	8 mo.	1	++++
5	R. E.	1 yr.	1	++++
6	D. M.	3 yr.	1	+++
7	W. L.	3 yr.	1	+++
8	S. M.	8 mo.	1	++++
9	B. S.	6 mo.	1	++++
10	C. L.	8 mo.	1	++
11	J. S.	2½ yr.	1	++++
12	W. G.	3 yr.	1	+++
13	C. S.	3½ yr.	1	+++
14	B. B.	1½ yr.	1	++++
15	L. W.	3½ yr.	1	++++
16	J. M.	2½ yr.	1	++++

Number	Name	Age	Amount, Cc.	Complement Fixation
17	L. B.	11 mo.	1	+ + +
18	C. S.	3 yr.	1	+ + + +
19	R. E.	10 mo.	1	+ + + +
20	M. H.	7 mo.	1	+ + + +
21	E. L.	17 mo.	1	+ + + +
22	P. H.	2 yr.	1	+ + + +
23	J. H.	1 yr.	1	+ +
24	K. M.	3½ yr.	1	+ + + +
25	J. C.	2½ yr.	1	+ + + +
26	J. B.	5 yr.	1	+ + + +
27	L. D.	1 yr.	1	+ + +
28	J. B.	2½ yr.	1	+ +
29	R. S.	1 yr.	1	+ + + +
30	P. A.	9 mo.	1	+ + + +
31	J. P.	10 mo.	1	+ + + +
32	B. P.	8 mo.	1	+ + + +
33	M. R.	5 yr.	1	+ + + +
34	P. T.	8 mo.	1	+ + + +
35	R. L.	1½ yr.	1	+ + + +
36	C. L.	2½ yr.	1	+ + + +
37	M. B.	9 mo.	1	+ + + +
38	H. H.	11 mo.	1	+
39	W. M.	18 mo.	1	+ + + +
40	M. P.	12 mo.	1	+ + + +
41	J. W.	6 yr.	1	+ + + +
42	N. C.	6 yr.	1	+ + + +
43	J. B.	20 mo.	1	+ + + +
44	C. D.	8 mo.	1	+ + + +
45	J. S.	5 yr.	1	+ + + +
46	C. P.	10 mo.	1	+ + + +
47	M. P.	1 yr.	1	+ + + +
48	V. T.	3 yr.	1	+ + + +
49	E. R.	7 yr.	1	+ + +
50	L. C.	2 yr.	1	+ + + +
51	L. C.	1 yr.	1	+ + + +
52	J. J.	8 mo.	1	+ + + +
53	H. H.	7 mo.	1	+ + + +
54	H. F.	11 mo.	1	+ + +
55	D. C.	9 mo.	1	+ +
56	B. D.	9 mo.	1	+ + + +
57	B. D.	9 mo.	1	+ + + +
58	G. K.	1 yr.	1	+ + +
59	L. K.	1 yr.	1	+ + + +
60	B. W.	2½ yr.	1	+ + + +
61	J. K.	2 yr.	1	+ +
62	L. H.	7 mo.	1	+ + + +
63	R. M.	3 yr.	1	+ + + +
64	R. F.	2½ yr.	1	+ + + +
65	J. A.	13 mo.	1	+ + + +
66	B. M.	1 yr.	1	+ + + +
67	W. T.	1½ yr.	1	+ + + +
68	B. B.	2½ yr.	1	+
69	W. E.	1 yr.	1	+ + + +
70	M. B.	1½ yr.	1	+ + + +
71	M. R.	1½ yr.	1	+ + + +
72	J. B.	4 yr.	1	−
73	S. L.	2 yr.	1	+ + + +
74	M. L.	14 mo.	1	+ + + +
75	W. B.	2 yr.	1	+ + + +
76	M. B.	9 yr.	1	−
77	B. B.	6 yr.	1	+ +
78	B. H.	4 yr.	1	+ + + +
79	D. H.	2 yr.	1	+ +
80	C. S.	6 mo.	1	+ + + +
81	H. S.	1 yr.	1	+ + + +
82	S. S.	2 yr.	1	+ + + +
83	D. S.	8 mo.	1	+ + + +
84	J. H.	7 mo.	1	+ + + +
85	Z. B.	8 yr.	1	+ +
86	D. B.	6 yr.	1	+ + + +
87	W. C.	20 mo.	1	+ + + +
88	J. B.	9 mo.	1	+ + + +
89	M. W.	16 mo.	1	+ +
90	J. D.	10 mo.	1	+ + + +
91	N. G.	10 mo.	1	+ + + +
92	M. J.	8 mo.	1	+ + + +
93	B. W.	6 mo.	1	+ + + +
94	T. P.	3½ yr.	1	+ + + +
95	P. G.	2 yr.	1	+ +
96	B. J.	2½ yr.	1	+ + + +

Number	Name	Age	Amount, Cc.	Complement Fixation
97	B. W.	5 yr.	1	+
98	B. W.	3 yr.	1	++++
99	D. C.	7 mo.	1	—
100	L. W.	7 mo.	1	—
101	J. M.	10 mo.	1	—
102	R. M.	15 mo.	1	—
103	I. G.	9 mo.	1	++++
104	P. J.	4 yr.	1	—
105	E. J.	6 yr.	1	—
106	B. C.	7 mo.	1	—
107	V. C.	3 yr.	1	++++
108	B. J.	3½ yr.	1	++++
109	W. J.	1 yr.	1	++++
110	M. J.	5 yr.	1	++++
111	F. A.	2½ yr.	1	++++
112	M. W.	1 yr.	1	++++

Number	Name	Age	Amount of Vaccine, Cc.*	Complement Fixation	Antitoxin Titer
1	J. M.	2½ yr.	1	++++	—0.002
2	C. S.	3 yr.	1	++++	0.01
3	R. E.	10 mo.	1	++++	0.002
4	M. W.	7 mo.	1	++++	IQ
5	E. C.	17 mo.	1	++++	—0.002
6	P. H.	2 mo.	1	++++	0.002
7	J. H.	1 yr.	1	++	0.002
8	K. M.	3 yr.	1	++++	0.002
9	J. C.	2 yr.	1	++++	0.002
10	F. D.	5 yr.	1	++++	0.01
11	L. D.	1 yr.	1	+++	0.01
12	J. B.	2 yr.	1	++	—0.002
13	R. S.	1 yr.	1	++++	0.01
14	P. A.	9 mo.	1	++++	0.1
15	P. C.	10 mo.	1	++++	1.0
16	B. P.	8 mo.	1	++++	0.1
17	M. R.	5 yr.	1	++++	0.01
18	P. F.	8 yr.	1	++++	0.002
19	R. L.	1½ yr.	1	++++	0.01
20	C. L.	2½ yr.	1	++++	0.1
21	M. C.	9 mo.	1	++++	0.002
22	H. H.	11 mo.	1	+	0.002
23	W. M.	18 mo.	1	++++	0.002
24	M. P.	1 yr.	1	++++	0.1
25	J. W.	6 yr.	1	++++	0.1
26	M. C.	6 yr.	1	++++	0.002
27	J. B.	1 yr.	1	++++	0.002
28	M. J.	6 mo.	1	++++	.....
29	C. D.	8 mo.	1	++++	0.2
30	M. W.	16 mo.	1	++	1.0
31	J. D.	10 mo.	1	++++	.....
32	M. G.	10 mo.	1	+++	.....
33	R. G.	6 mo.	1	++++	0.002

* All patients above 6 months of age received 1 cc. of alum-precipitated diphtheria toxoid at the state health department. The exact dates were not obtained.

145 patients
9 negative complement fixations—6%
136 positive complement fixations—94%
107 ++++ complement fixations—74%

5. PERTUSSIS VACCINE, PROPHYLACTIC (20 BILLION COUNT)

The vaccine contained 20 billion pertussis organisms per cubic centimeter. The children for whom results are tabulated here each received a total of 5 cc. given in the following manner: 1 cc., 2 cc. and 2 cc. at weekly intervals. The local and systemic reactions were very mild. These patients received 1.5 cc. of diphtheria toxoid at 6 months and at 7 months. Schick tests were done three months after the last injection of toxoid. The titrations and complement fixation tests were made one week after the last injection of pertussis vaccine. There is a marked variation in the titers, but all the Schick reactions were negative except 1. Titrations were not made for the first 25 patients listed.

Number	Name	Age	Amount of Vaccine, Cc.	Complement Fixation	Amount of Diphtheria Toxoid, Cc.	Antitoxin Titer	Schick Reaction
1	F. M.	8 mo.	5	++++	...	.....	.....
2	C. R.	8 mo.	5	++++	...	.....	.....
3	R. S.	8 mo.	5	++++	...	.....	.....
4	J. G.	8 mo.	5	++++	...	.....	.....
5	F. S.	8 mo.	5	+	...	.....	.....
6	M. B.	11 mo.	5	++++	...	.....	.....
7	D. B.	11 mo.	5	++++	...	.....	.....
8	R. B.	11 mo.	5	++++	...	.....	.....
9	J. F.	8 mo.	5	++++	...	.....	.....
10	C. P.	11 mo.	5	+	...	.....	.....
11	M. G.	11 mo.	5	+	...	.....	.....
12	L. L.	8 mo.	5	++++	...	.....	.....
13	A. F.	8 mo.	5	++++	...	.....	.....
14	T. C.	7 mo.	5	++++	...	.....	.....
15	N. O.	8 mo.	5	++++	...	.....	.....
16	G. H.	8 mo.	5	++++	...	.....	.....
17	N. H.	8 mo.	5	++++	...	.....	.....
18	N. H.	8 mo.	5	++++	...	.....	.....
19	B. M.	8 mo.	5	++++	...	.....	.....
20	S. B.	4 mo.	5	++++	...	.....	.....
21	R. B.	8 mo.	5	++++	...	.....	.....
22	J. H.	8 mo.	5	++	...	.....	.....
23	M. H.	8 mo.	5	++++	...	.....	.....
24	W. K.	8 mo.	5	++++	...	.....	.....
25	G. D.	9 mo.	5	++++	...	.....	.....
26	F. C.	8 mo.	5	+++	3	IQ	Neg.
27	M. F.	8 mo.	5	++++	3	0.01	Neg.
28	C. W.	9 mo.	5	++	3	0.01	Neg.
29	V. M.	8 mo.	5	++++	3	0.01	Neg.
30	E. A.	8 mo.	5	+++	3	0.01	Neg.
31	R. B.	9 mo.	5	—	3	0.001	.....
32	J. C.	8 mo.	5	++++	3	0.01	.....
33	B. C.	8 mo.	5	++	3	0.01	.....
34	J. C.	11 mo.	5	++++	3	0.01	.....
35	D. H.	8 mo.	5	+	3	0.002	Neg.
36	J. M.	8 mo.	5	+++	3	0.01	Neg.
37	J. R.	8 mo.	5	+++	3	0.01	Neg.
38	P. W.	4 yr.	5	+++	3	—0.002	Pos.
39	K. W.	8 mo.	5	+	3	0.01	Neg.
40	C. C.	2 yr.	5	+	3	0.01	Neg.
41	F. P.	8 mo.	5	++++	3	0.01	.....
42	C. R.	10 mo.	5	++++	3	0.1	Neg.
43	V. T.	11 mo.	5	++++	3	0.1	Neg.
44	A. A.	11 mo.	5	++++	3	0.001	Neg.
45	K. C.	9 mo.	5	+++	3	0.01	Neg.
46	B. H.	11 mo.	5	++++	3	0.001	.....
47	L. H.	23 mo.	5	++++	3	0.1	.....
48	D. M.	11 mo.	5	++++	3	0.01	.....
49	S. A.	11 mo.	5	++++	3	0.01	Neg.
50	F. D.	11 mo.	5	++++	3	0.01	Neg.
51	R. M.	8 mo.	5	++++	3	0.01	Neg.
52	J. M.	8 mo.	5	+	3	0.01	Neg.
53	E. A.	8 mo.	5	++++	...	.....	.....
54	W. L.	11 mo.	5	++++	3	0.1	Neg.
55	P. P.	11 mo.	5	+++	...	0.002	.....
56	S. H.	11 mo.	5	++++	3	0.002	Neg.
57	P. B.	8 mo.	5	++++	3	0.002	Neg.
58	S. E.	8 mo.	5	++++	3	0.1	Neg.
59	S. J.	8 mo.	5	++++	3	0.002	Neg.
60	M. R.	8 mo.	5	++++	3	0.01	Neg.
61	J. D.	8 mo.	5	++++	3	0.1	Neg.
62	E. H.	8 mo.	5	++++	3	.....	.....
63	N. H.	8 mo.	5	++++	3	0.2	Neg.
64	E. M.	8 mo.	5	++++	3	0.002	Neg.
65	R. P.	8 mo.	5	++++	...	.....	.....
66	W. S.	8 mo.	5	++++	3	0.1	Neg.
67	N. B.	8 mo.	5	++++	3	0.2	Neg.
68	P. B.	8 mo.	5	++++	3	0.002	.....
69	C. E.	8 mo.	5	++++	3	0.2	Neg.
70	G. G.	8 mo.	5	++++	3	0.01	Neg.
71	N. H.	8 mo.	5	++++	3	0.02	Neg.
72	E. R.	8 mo.	5	++++	3	0.01	Neg.
73	B. R.	8 mo.	5	++++	3	0.05	Neg.
74	S. T.	8 mo.	5	++++	3	0.002	Neg.
75	B. T.	4 yr.	5	++++	3	0.05	Neg.
76	J. T.	6 yr.	5	++++	3	0.2	Neg.
77	N. T.	8 mo.	5	++++	3	0.02	.....
78	H. Y.	8 mo.	5	++++	3	0.1	.....
79	M. A.	8 mo.	5	++++	3	0.01	.....
80	C. A.	8 mo.	5	++++	3	0.01	Pos.

Number	Name	Age	Amount of Vaccine, Cc.	Complement Fixation	Amount of Diphtheria Toxoid, Cc.	Antitoxin Titer	Schick Reaction
81	P. A.	8 mo.	5	++++	3	—0.002	.....
82	B. B.	8 mo.	5	++++	3	0.01	.....
83	E. G.	8 mo.	5	++++	3	0.01	.....
84	J. H.	8 mo.	5	++++	3	0.002	.....
85	E. M.	8 mo.	5	++++	3	—0.002	Neg.
86	J. M.	8 mo.	5	++++	3	0.01	.....
87	K. O.	8 mo.	5	++++	3	—0.002	.....
88	N. O.	8 mo.	5	++++	3	0.02	Neg.
89	B. T.	8 mo.	5	++++	3	0.1	.....
90	S. B.	8 mo.	5	++++	3	0.1	Neg.
91	R. M.	10 mo.	5	++++	3	0.002	Neg.
92	R. M.	10 mo.	5	++++	3	0.002	Neg.
93	B. R.	8 mo.	5	++++	3	0.01	Neg.
94	J. S.	8 mo.	5	+++	3	0.002	Neg.
95	D. S.	8 mo.	5	++++	3	0.002	Neg.
96	S. A.	8 mo.	5	+++	3	0.2	Neg.
97	H. A.	8 mo.	5	++	3	0.002	Neg.
98	B. W.	3 yr.	5	++++	3	0.002	Neg.
99	R. P.	3 yr.	5	++++	3	.....	.....
100	A. B.	3 yr.	5	++++	...	.....	.....

100 complement fixation tests
77 ++++ complement fixations—77%
99+ or better—99%
69 titrations
47 above —0.002—68.2%

6. PERTUSSIS VACCINE, PROPHYLACTIC (40 BILLION COUNT)

At the meeting of the American Medical Association in New York on June 10, 1940, there was a suggestion that the bacteria count in pertussis vaccine should be reduced from 20 billion to 15 billion, as severe reactions to the 20 billion count vaccine had been reported. Twenty-six of the pediatricians of Atlanta were questioned as to the type of vaccine used and the reactions observed. Two continued to use 10 billion count vaccine. Twenty-four used the 20 billion count vaccine. They stated that the reactions were not any more severe than with the 10 billion count vaccine, and they seemed to feel that the reactions were really less severe, as the amount of vaccine used was only half as great.

Subsequently a vaccine with a 40 billion count was made up. Each child received 1 cc. each week for three injections. The local and systemic reactions were not as marked as with the 10 billion or 20 billion count vaccine, as the volume used was so small. The patients received a total of 120 billion organisms, with the following results:

Number	Name	Age	Amount, Cc.	Complement Fixation
1	P. B.	3 yr.	3	—
2	E. W.	10 mo.	3	+++
3	C. H.	2 yr.	3	++++
4	J. S.	15 mo.	3	++++
5	J. G.	14 mo.	5	++++
6	B. S.	6 yr.	3	+++
7	R. M.	1 yr.	3	++++
8	J. S.	3 yr.	3	++++
9	J. A.	1 yr.	3	++++
10	S. C.	8 mo.	3	++++
11	C. C.	8 mo.	3	++++
12	C. F.	7 mo.	3	++++
13	H. S.	19 mo.	3	++++
14	W. A.	6 mo.	3	++++
15	M. H.	2 yr.	3	++++
16	W. H.	6 yr.	3	—
17	L. H.	3 yr.	3	—
18	J. H.	1 yr.	3	—
19	P. M.	8 mo.	3	++++
20	J. W.	4 yr.	3	++++

Number	Name	Age	Amount, Cc.	Complement Fixation
21	J. W.	7 mo.	3	++
22	C. A.	8 mo.	3	++++
23	G. A.	4 yr.	3	++++
24	H. M.	1 yr.	3	++++
25	O. P.	1 yr.	3	++++
26	D. C.	14 mo.	3	++++
27	M. B.	3½ yr.	3	++++
28	W. C.	15 mo.	3	++++
29	L. W.	2½ yr.	3	++++
30	M. C.	3 yr.	3	++++
31	B. C.	5 yr.	3	++++
32	P. C.	20 mo.	3	++++
33	C. H.	3 yr.	3	++++
34	P. H.	7 mo.	3	++++
35	N. E.	21 mo.	3	++++
36	J. M.	8 mo.	3	+++
37	M. M.	4½ yr.	3	+++
38	M. C.	3½ yr.	3	++++
39	E. M.	4½ yr.	3	++++
40	A. W.	2 yr.	3	++++
41	B. W.	4 yr.	3	++++
42	P. B.	3 yr.	3	+++
43	M. B.	1½ yr.	3	++++
44	G. B.	7 yr.	3	+++
45	E. A.	2 yr.	3	++++
46	M. P.	1 yr.	3	++++
47	J. M.	1 yr.	3	++++
48	L. A.	1½ yr.	3	++++
49	S. F.	2½ yr.	3	++++
50	L. G.	14 mo.	3	+++
51	J. N.	15 mo.	3	+++
52	J. M.	10 mo.	3	+++
53	M. M.	10 mo.	3	++++
54	D. W.	2 yr.	3	+++
55	C. A.	4 yr.	3	++++
56	J. H.	6 mo.	3	+++
57	B. Y.	10 mo.	3	+++
58	D. W.	8 mo.	3	++++
59	J. C.	5 yr.	3	++++
60	A. C.	2 yr.	3	+++
61	L. W.	6 wk.	3	−
62	M. M.	7 yr.	3	++++
63	S. M.	5 yr.	3	++++
64	J. H.	9 mo.	3	++++
65	S. P.	1 yr.	3	++++
66	S. Y.	2 yr.	3	++++
67	W. B.	6 mo.	3	+++
68	J. E.	16 mo.	3	++++
69	B. E.	4 yr.	3	++++
70	J. D.	22 mo.	3	++++
71	C. W.	7 mo.	3	++++
72	J. S.	2 yr.	3	++++
73	W. S.	4 yr.	3	++++
74	G. B.	3 yr.	3	++++
75	W. B.	10 mo.	3	+++
76	M. H.	6 mo.	3	++++
77	G. J.	9 mo.	3	++++
78	J. S.	7 mo.	3	++++

78 patients
5 negative complement fixations—6%
73 positive complement fixations—94%
57 ++++ complement fixations—73%

Patients numbered 16, 17 and 18 (W. H., L. H. and J. H.) had negative complement fixation. These children were in the same family, and the fact that all had negative complement fixation represents an unusual condition. It required as much as 4 cc. of the 40 billion count vaccine to immunize these 3 children. If the data on these children were eliminated, the percentage of 4 plus complement fixation reactions would have been much larger in this group than in the groups receiving the other vaccines.

7. COMBINED VACCINE AND DIPHTHERIA AND TETANUS TOXOIDS, ALUM PRECIPITATED, NO. 5778

This vaccine contained 20 billion pertussis organisms per cubic centimeter and 20 Lf units of diphtheria toxoid, and the tetanus toxoid used in this lot had a potency of approximately 10,000 minimum lethal doses per cubic centimeter. The vaccine was given in doses of 0.2 cc., 0.4 cc. and 0.4 cc. at weekly intervals, a total of 1 cc. Complement fixation and agglutination tests and titrations were done one week after the last injection. Schick tests were done three months after the last injection. The following results were obtained:

Number	Name	Age	Schick Reaction	Amount, Cc.	Complement Fixation	Agglutination	Diphtheria Antitoxin Titer	Tetanus Antitoxin Titer	Schick Reaction
1	B. M.	7 mo.	Pos.	1	++	++++	—0.002	0.003	Neg.
2	R. T.	10 mo.	Pos.	1	—	++++	0.02	0.003	Neg.
3	M. C.	22 mo.	Pos.	1	++++	++	0.05	0.003	Neg.
4	B. S.	17 mo.	Pos.	1	++++	++++	0.2	0.1	Neg.
5	T. H.	7 mo.	Pos.	1	++++	++++	0.2	0.1	Neg.
6	J. B.	2½ yr.	Pos.	1	++	++++	2.0	—0.003	Neg.
7	C. L.	6 mo.	Pos.	1	+	++	0.05	+0.1	Neg.
8	F. W.	5½ mo.	Pos.	1	+++	++++	0.002	+0.003	Neg.
9	C. B.	1 yr.	Pos.	1	+++	+	0.002	+0.003	Neg.
10	P. S.	8 mo.	Pos.	1	+++	+	0.002	—0.003	Neg.
11	E. R.	2 yr.	Pos.	1	++++	++++	0.02	+0.1	Neg.
12	R. R.	6 mo.	Pos.	1	++	—	0.002	0.003	Neg.
13	A. M.	2½ yr.	Pos.	1	—	++++	0.05	+0.1	Neg.
14	F. M.	14 mo.	Pos.	1	+	++	0.2	+0.1	Neg.
15	J. C.	5 mo.	Pos.	1	++	++++	—0.002	+0.1	Neg.
16	L. R.	4 mo.	Pos.	1	Ac	—	—0.002	0.017	Neg.
17	J. G.	6 mo.	Pos.	1	++++	++++	0.002	0.003	Neg.
18	P. B.	1 yr.	Pos.	1	++++	++++	0.002	—0.003	Neg.
19	M. H.	8 mo.	Pos.	1	++++	++++	0.002	0.017	Neg.
20	S. M.	6 mo.	Pos.	1	+++	++++	0.002	+0.01	Neg.
21	C. H.	6 mo.	Pos.	1	+++	+++	0.002	0.003	Neg.
22	M. C.	2 yr.	Pos.	1	Ac	—	0.002	—0.003	Neg.
23	J. A.	18 mo.	Pos.	1	Ac	++++	0.002	—0.003	Neg.
24	R. R.	11 mo.	Pos	1	++++	++++	0.002	+0.017	Neg.
25	H. C.	6 mo.	Pos.	1	++	—	0.002	0.003	Neg.
26	J. S.	2 yr.	Pos.	1	+++	+++	0.002	0.003	Neg.
27	B. C.	8 mo.	Pos.	1	++++	++++	—0.002	+0.01	Neg.
28	B. J.	8 mo.	Pos.	1	Ac	—	0.002	0.01	Neg.
29	G. B.	7 mo.	Pos.	1	+++	+++	—0.002	—0.003	Neg.
30	H. G.	6 mo.	Pos.	1	++	++++	0.002	+0.01	Neg.
31	W. W.	12 mo.	Pos.	1	+++	+++	+0.002	+0.003	Neg.
32	G. B.	16 mo.	Pos.	1	++++	++++	0.002	0.003	Neg.
33	R. T.	6 mo.	Pos.	1	Ac	++++	0.002	0.01	Neg.
34	A. D.	4 mo.	Pos.	1	—	++++	0.002	0.003	Neg.
35	P. S.	7 mo.	Pos.	1	Ac	—	0.002	.....	Neg.
36	G. C.	6 mo.	Pos.	1	—	—	0.002	0.01	Neg.
37	N. B.	18 mo.	Pos.	1	++++	++++	0.002	.....	Neg.
38	B. D.	6 mo.	Pos.	1	Ac	++++	0.05	.....	Neg.
39	S. D.	6 mo.	Pos.	1	—	—	0.002	0.01	Neg.
40	B. P.	5 mo.	Pos.	1	Ac	++++	.....	.....	Neg.

32 complement fixation tests
5 negative fixations—15.6%
27 positive fixations—84.4%
11 ++++ fixations—34.4%

40 agglutination tests
8 negative agglutinations—20%
32 positive agglutinations—80%
23 ++++ agglutinations—57.5%

39 diphtheria antitoxin titrations
35 above —0.002—89.7%

36 tetanus antitoxin titrations
30 above —0.003—83.3%

AGGLUTINATION TEST

Since 1933 my associates and I have used the complement fixation test to determine the antibody response to the pertussis vaccine, using the 4 plus complement fixation as the required reaction to insure immunity, as this is the degree of fixation present after an attack of the disease.

In a group of 1,170 patients with 4 plus complement fixation there has not been a single attack of whooping cough. Some persons have required for immunization as much as 14 cc. of Sauer's 10 billion count vaccine, 7 cc. of the 20 billion count vaccine, 4 cc. of the 40 billion count vaccine, 2.5 cc. of the alum-precipitated vaccine no. 4817 B, 1.5 cc. of the alum-precipitated vaccine no. 4817 A or 8 cc. of combined diphtheria toxoid and pertussis vaccine B-5325.

Without some way to test patients receiving the vaccine, one cannot be sure the patient is immunized. The complement fixation test seems to be a sure method, but it requires a large amount of equipment and time.

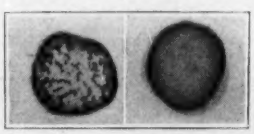

Fig. 1.—At left, 4 plus agglutination; at right, negative reaction.

Since March 1941 the bedside agglutination test has been used to make a comparative study of the agglutination test with the complement fixation test. Group 7 shows an example of this comparison, from which very similar results will be noted. According to the Lilly Research Laboratories, the following technic for making the test is satisfactory: "Such tests utilize a single drop of the respective antigen, suitably prepared and stained blue, and a single drop of the patient's blood, obtained from the finger as for blood counts. These two drops are mixed as a ½ inch (1.3 cm.) circle on a piece of white glazed cardboard the size of a microscope slide and tilted back and forth for one minute, at which time any visible agglutination is read off."

In making tests for this study serum was used instead of blood. Six drops of blood was collected in a small tube, and after the clot retracted 1 drop of serum was added to 1 drop of antigen on white cardboard.

The agglutination test should be made from one to two months after treatment with the vaccine. The agglutination reaction reaches its height much later than the complement fixation reaction. As the test has been employed for only a few months with such excellent results,

its use should be continued. As to its value as a diagnostic method, I have not had enough experience to make a statement, but in the cases in which it was used the reaction did not become positive until the fourth week. In cases in which there is doubt as to the diagnosis of whooping cough, it should be of great value.

CONCLUSION

Since March 1933 my associates and I at the Central Presbyterian Church Clinic for Children have conducted a continuous clinic for treating whooping cough and studying immunization. Comparative

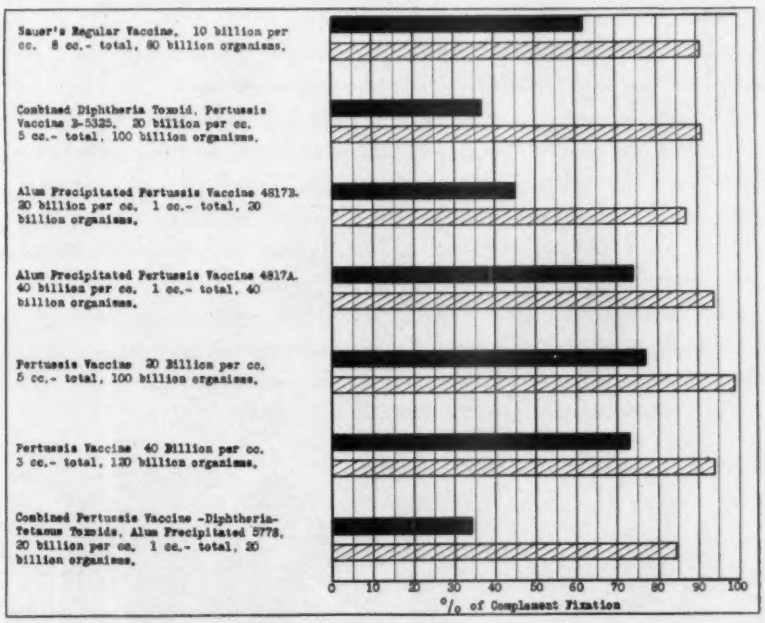
Sauer's Regular Vaccine. 10 billion per cc. 8 cc.- total, 80 billion organisms.
Combined Diphtheria Toxoid, Pertussis Vaccine B-5325. 20 billion per cc. 5 cc.- total, 100 billion organisms.
Alum Precipitated Pertussis Vaccine 4817B. 20 billion per cc. 1 cc.- total, 20 billion organisms.
Alum Precipitated Pertussis Vaccine 4817A. 40 billion per cc. 1 cc.- total, 40 billion organisms.
Pertussis Vaccine 20 Billion per cc. 5 cc.- total, 100 billion organisms.
Pertussis Vaccine 40 Billion per cc. 3 cc.- total, 120 billion organisms.
Combined Pertussis Vaccine -Diphtheria-Tetanus Toxoids, Alum Precipitated 5778. 20 billion per cc. 1 cc.- total, 20 billion organisms.
0 10 20 30 40 50 60 70 80 90 100
% of Complement Fixation

Fig. 2.—Comparison of results obtained with different vaccines. The ruled bars indicate the percentage of patients with positive complement fixation; the solid bars, the percentage with 4 plus complement fixation.

results obtained from the use of the various vaccines are presented in the accompanying chart (fig. 2). From the studies that have been made the following conclusions are reached:

1. A potent vaccine is necessary.

2. All children are not immunized alike, and no standard dosage can be prescribed.

3. There should be some method of determining the degree of immunity.

4. The complement fixation test is accurate but is complicated.

5. The bedside agglutination test seems to be the answer to this problem, as it produces approximately the same results as the complement fixation test.

6. To obtain immunization with Sauer's regular pertussis vaccine (10 billion count), it is necessary to give as much as 14 cc. in some cases. With 20 billion count pertussis vaccine the maximum requirement is 7 cc.; with 40 billion count pertussis vaccine, 4 cc.; with alum-precipitated 20 billion count pertussis vaccine, 2.5 cc.; with 40 billion count alum-precipitated pertussis vaccine, 1.5 cc.; with combined diphtheria toxoid and pertussis vaccine 20 billion count, 8 cc.; with combined pertussis vaccine and diphtheria and tetanus toxoids, alum precipitated, 20 billion count, 2.5 cc.

7. The effectiveness of the vaccine is determined not by the number of organisms received but by the rate of absorption.

8. Therefore, the 40 billion count pertussis vaccine or the 40 billion count alum-precipitated pertussis vaccine gives the best results.

9. The combined diphtheria toxoid and pertussis vaccine produces good results, but the pertussis organism count should be increased from 20 billion to 40 billion. The amount of diphtheria toxoid is sufficient to give a negative Schick reaction.

10. Combined pertussis vaccine and diphtheria and tetanus toxoids, alum precipitated, shows excellent possibilities for the giving of three immunizations in one; however, the pertussis organism count in this vaccine should be increased to 40 billion.

SPREAD OF POLIOMYELITIS VIRUS ALONG AXONS OF PERIPHERAL NERVES

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It is of great importance to know (1) how poliomyelitis virus enters the human body and (2) how it passes into the central nervous system.

Hurst [1] has demonstrated that poliomyelitis can be produced in monkeys by injection of the virus into the sciatic nerve. His results established the theory that poliomyelitis virus spreads by way of axonic pathways. We, as well as others, repeated Hurst's experiments and confirmed his findings. However, we were not uniformly successful when subpassage of the virus was attempted by way of other peripheral nerves (Toomey [2]).

The fact that poliomyelitis was not uniformly produced when the virus was injected in the peripheral nerves of monkeys was of no particular importance, since it was realized that even in nature the disease does not occur in all animals or human beings. It has been our belief that the virus has nearly an obligate affinity for naked gray fibers or for the gray-fibered axis-cylinders of peripheral nerves. Thus, the virus might be picked up (1) by the axis-cylinders of cranial nerves, by which it would be brought directly to the medullary area, (2) by the gray fibers of the sympathetic system, along which it would spread to the somatic nerves and thence to the cord, or (3) by the fibers of the parasympathetic nervous system, whence it would pass along the vagus nerve to the medulla. Such a belief rests on the theory of axonic spread.

Four years later we repeated Hurst's experiments in Macaca mulatta monkeys by injecting the virus into their sciatic nerves. The disease did not develop in a single one of 10 animals thus inoculated, although quadriplegia was produced in the same animals and other control animals

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From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

1. Hurst, E. W.: Further Contribution to Pathogenesis of Experimental Poliomyelitis Inoculation into Sciatic Nerve, J. Path. & Bact. **33**:1133, 1930.

2. Toomey, J. A.: Experiments with Poliomyelitis Virus, Proc. Soc. Exper. Biol. & Med. **32**:1185, 1935.

a month later when they were all intracerebrally inoculated with the same amount and dilution of virus. When the experiment was repeated, the results were the same. Harrison and Woolpert [3] obtained similar results.

Failure to produce the disease in normal monkeys by way of the sciatic nerve was disturbing. The results of these experiments were contrary to those of previous ones. Since the theory of axonic spread was based on similar experiments which had been successful, consistently negative results of repeated experiments would tend to make this conception of pathogenesis questionable. It was necessary to obtain a plausible reason for the subsequent negative results or to abandon the evidence which had heretofore been considered the very foundation for the belief that the virus spreads by way of the axis-cylinders.

In seeking an explanation, we found that our virus strain had decreased in virulence, since it had become necessary during the past four years to increase its dose and concentration in order to produce quadriplegia in every instance. Since we, as well as Harrison and Woolpert, had used purified virus in most of our experiments, it was possible that the methods used to accomplish purification might have robbed the virus of some of its virulence. This could not be the case, however, since Harrison and Woolpert obtained the same results with unpurified virus.

Since the virus we used still produced experimental poliomyelitis in 100 per cent of the monkeys into which it was injected intracerebrally, it was thought that there may have been some quantitative changes in virulence of the strain which was not apparent when the test animal was inoculated intracerebrally. In short, the disease is more easily produced intracerebrally.

It was decided to determine whether there were differences by comparing the effects which followed injections of two virus strains into the sciatic nerve. We were fortunate enough to secure from another laboratory a subpassage specimen of the same virus strain that we had used for years. Thus, we were able to compare samples of the same strain which had been carried by two different laboratories.

Strain I (Flexner's M. V. strain) was obtained from Dr. Sabin, of the University of Cincinnati, who in turn obtained it from the Rockefeller Institute. Strain II (Flexner's M. V. strain) came from the department of bacteriology of the University of Chicago. This laboratory had obtained its original material from Dr. Rhoads, of the Rockefeller Institute.[4]

3. Harrison, J. A., and Woolpert, O. C.: Intraneural Injections of Serum as a Barrier to Migration of Virus in Experimental Poliomyelitis, J. Infect. Dis. **65**:214, 1939.

4. Gordon, F. B.: Personal communication to the authors.

EXPERIMENT SERIES 1

The objective of the experiments in series 1 was to compare the results following injections of these two virus strains into the sciatic nerve in Macaca mulatta monkeys.

Methods and Materials.—When an injection was to be made into the sciatic nerve, the left thigh of the monkey was shaved and while the animal was under general anesthesia the skin and muscles over the sciatic notch were turned backward and laterally. The sciatic nerve was exposed, and a probe was passed under the nerve to hold it in position. The nerve was then gently clamped with a hemostat at three places above and three below the anchoring instrument, care being taken not to split the nerve sheath. A 26 gage needle fitted to a tuberculin syringe

TABLE 1.—*Results of Experiments in Series 1 (Experiments 1 to 6 Inclusive)*

	Strain I Sciatic Nerve		Strain I Intracerebral		Strain II Sciatic Nerve		Strain II Intracerebral	
Experiment No.	Monkey No.	Result	Monkey No.	Result	Mon. key No.	Result	Monkey No.	Result
1	1	Quadriplegia 6 days	3	Quadriplegia 5 days	2*	Furred only	4	Quadriplegia 7 days
2	5	Quadriplegia 8 days	7	Quadriplegia 6 days	6*	Furred only	8	Quadriplegia 8 days
3	9	Quadriplegia 7 days	11	Quadriplegia 5 days	10*	Negative	12	Quadriplegia 13 days
4	13	Quadriplegia 7 days	15	Quadriplegia 6 days	14*	Negative	16	Quadriplegia 10 days
5	17	Quadriplegia 6 days	19	Quadriplegia 6 days	18*	Negative	20	Quadriplegia 7 days
6	21	Quadriplegia 13 days	23	Quadriplegia 5 days	22*	Negative	24	Quadriplegia 8 days

* Monkeys 2, 6, 10, 14, 18 and 22 were later inoculated intracerebrally with 0.5 cc. of a 1 per cent suspension of strain II; all had quadriplegia in from six to ten days following the injection.

was inserted into the center of the nerve pointing cephalad, and one-half the virus suspension was slowly injected. The needle was withdrawn and reinserted with the point caudad, and the remainder of the virus was injected. Five-tenths cubic centimeters of a 10 per cent suspension was the total dose injected. This was the same in all instances, except in the last experiment, as noted. As the nerve became infiltrated with virus suspension, it became chalk white. After the injection, which had to be made cautiously and slowly in order to avoid rupture, the nerve was dropped back into its bed. Hemorrhage was controlled with hemostasis. The incision in the skin was closed with metal clips, and collodion was poured over the closed area.

Six experiments were done, 4 animals being used for each experiment. In each instance, 1 monkey was given a suspension of virus strain I intrasciatically; 1, strain I intracerebrally; 1, strain II intrasciatically; and 1, strain II intracerebrally. The animals were observed for at least twenty-one days following the injection.

Results.—Both strain I and strain II caused quadriplegia in every instance when injected intracerebrally (table 1). Objectively, the clinical picture was the same after the injections of the two strains. Poliomyelitis developed in all animals inoculated with strain I by way of the sciatic nerve while none of the 6 animals inoculated with strain II by this route became paralyzed. The fur of 2 of the latter was ruffled about the eighth day after the injection. Nevertheless, these 6 were not immune, for when they were inoculated intracerebrally one month later with the same amount and dilution of virus suspension, quadriplegia developed in all 6 animals in from six to ten days after the injection.

It was clear that strain II, Flexner's M. V. strain carried in our laboratory, was not so potent as strain I, Flexner's M. V. strain carried in another laboratory (Sabin).

The results of these experiments were clearcut and checked with our recent results and those of Harrison and Woolpert. It was clear also that when we employed a virulent type of virus, the Sabin subpassage specimen of Flexner's M. V. strain, the disease was easily produced.

EXPERIMENT SERIES 2

The purpose of the experiments in series 2 was to ascertain why our strain was not so potent as the strain received from Dr. Sabin.

Our strain had been transplanted on an average of every five or six months. Delayed transfer might decrease the virulence. It was noticed in other experiments that repeated transfers tended to enhance the virulence of the virus. Were this true, then a greater number of animals the peripheral nerves of which were inoculated with this type of rapidly transferred virus would come down with the disease, and the previous apparent differences in virulence between the two strains would become less marked. Our strain II virus was then transferred eight times within three months.

The same two strains were used in the same manner as in the experiments in series 1. The radial nerve was used this time as the peripheral nerve of entrance. Injection into this nerve presents a number of technical difficulties: (1) the nerve is ordinarily not so large as the sciatic nerve; (2) it may be split into two branches, and (3) it may be too small to hold 0.5 cc. of material without rupturing. Injections were made slowly and cautiously, but nevertheless there were leaks outside the nerve.

The frequent transfer of our virus strain II did make it more virulent (table 2). Injections into the radial nerve caused quadriplegia in 2 of 5 animals inoculated with virus strain I and in 4 of 5 inoculated with

virus strain II. The fact that it was not always possible to deliver a comparable dose into the radial nerve because of leakage made these results difficult to interpret. All of the control animals inoculated intracerebrally with either strain I or strain II had quadriplegia. A comparison control experiment was done in which the animals were inoculated via the sciatic nerve with comparable doses and suspensions of the two strains. Unlike our experience in the experiments in series 1, these animals too came down with the disease. The animals that did

TABLE 2.—*Results of Experiments in Series 2 (Experiments 7 to 12 Inclusive)*

	Strain I Radial Nerve		Strain I Intracerebral (Controls)		Strain II Radial Nerve		Strain II Intracerebral (Controls)	
Experiment No.	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result
7	25*	Furred	26	Quadriplegia 6 days	27	Quadriplegia 8 days	28	Quadriplegia 6 days
8	29*	Furred	30	Quadriplegia 6 days	31	Quadriplegia 8 days	32	Quadriplegia 6 days
9	33*	Furred	34	Quadriplegia 5 days	35	Bulbar spinal poliomyelitis 5 days	36	Quadriplegia 7 days
10	37	Quadriplegia 5 days	38	Quadriplegia 5 days	39*	Negative	40	Quadriplegia 8 days
11	41	Quadriplegia 12 days	42	Quadriplegia 6 days	43	Quadriplegia 5 days	44	Quadriplegia 7 days
	Sciatic Nerve		Sciatic Nerve		Sciatic Nerve		Sciatic Nerve	
Experiment No.	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result
12	45	Quadriplegia 5 days	46	Quadriplegia 6 days	47	Quadriplegia 9 days	48	Quadriplegia 7 days

* Monkeys 25, 29 and 33 were subsequently inoculated intracerebrally with 0.5 cc. of a 10 per cent suspension of strain 1 and came down with the disease in seven to twelve days after the injection; monkey 39 was inoculated intracerebrally with strain II and came down with the disease eight days later.

not have the disease after injection of the virus into the radial nerve were not protected, since one month later when they were intracerebrally inoculated with the virus they came down with poliomyelitis in from seven to twelve days.

EXPERIMENT SERIES 3

A third set of experiments was done to check the results of the second (table 3). Two animals inoculated with strain I by way of the radial nerve had poliomyelitis. One of those given an injection of strain II into the radial nerve died of tuberculosis some time later, but it did not have paralysis; the other had a delayed "take" and died subsequently of bulbar poliomyelitis and intestinal parasites. At this time,

either strain injected intracerebrally produced "takes" in all the monkeys. Control animals were given injections into the sciatic nerve, and all but 1 came down with the disease. The exception was one of the 2 that was given strain II. It later received strain II intracerebrally, and it came down with quadriplegia eight days later.

TABLE 3.—*Results of Experiments in Series 3 (Experiments 13 to 16 Inclusive)*

Experiment No.	Strain I Radial Nerve Monkey No.	Result	Strain I Intracerebral Monkey No.	Result	Strain II Radial Nerve Monkey No.	Result	Strain II Intracerebral Monkey No.	Result
13	49	Quadriplegia 4 days	50	Quadriplegia 9 days	51	Died of tuberculosis	52	Quadriplegia 7 days
14	53	Quadriplegia 8 days	54	Quadriplegia 10 days	55	Bulbar poliomyelitis and intestinal parasites	56	Quadriplegia 6 days
	Sciatic Nerve		Sciatic Nerve		Sciatic Nerve		Sciatic Nerve	
Experiment No.	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result	Monkey No.	Result
15	57	Quadriplegia 8 days	58	Quadriplegia 7 days	59	Quadriplegia 8 days	60	Quadriplegia 7 days
16	61	Quadriplegia 16 days	62	Quadriplegia 8 days	63*	Negative	64	Quadriplegia 8 days

* Monkey 63 was subsequently inoculated intracerebrally with strain II and had quadriplegia eight days later.

TABLE 4.—*Results of Experiments in Series 4 (Experiments 17 and 18)*

Experiment No.	Strain I Sciatic Nerve Monkey No.	Result	Strain I Intracerebral Monkey No.	Result	Strain II Sciatic Nerve Monkey No.	Result	Strain II Intracerebral Monkey No.	Result
17	65	Quadriplegia 10 days	66	Quadriplegia 6 days	67*	Negative	68	Quadriplegia 8 days
18	69	Quadriplegia 8 days	70	Quadriplegia 7 days	71*	Negative, save for slight tremor	72	Quadriplegia 7 days

* Monkeys 67 and 71 were subsequently inoculated intracerebrally with 0.1 cc. of a 10 per cent suspension of strain II. The disease developed in both animals within nine days.

EXPERIMENT SERIES 4

It was apparent that our virus strain II had become more virulent, probably with frequent passage. The difference, of course, might have been merely quantitative, since a large amount, 0.5 cc. of a 10 per cent suspension, was used as the injecting dose. It was thought best to make a test.

For that reason, another set of experiments was done the dose being only 0.1 cc. of a 10 per cent suspension of virus strains obtained from

the more recent passages. This amount was injected both into the sciatic nerve and intracerebrally, as in the previous experiments. The results were clearcut (table 4). Poliomyelitis developed in the animals inoculated either by way of the sciatic nerve or intracerebrally with strain I and in those inoculated intracerebrally with strain II. The disease did not develop in either of the animals inoculated by way of the sciatic nerve with strain II, although 1 had a slight tremor. Neither of the latter animals was protected, because one month later, when they were inoculated intracerebrally with strain II, quadriplegia developed in both in nine days.

COMMENT

The results of the experiments in series 1 were clearcut, showing a definite difference between the effects produced by the two strains. However, when the virus was submitted to frequent passages its virulence increased. Quantitative differences still were present, however, for when the doses of the increasingly virulent virus were decreased the differences between the two strains again became apparent. It can be seen that the negative results obtained by us and by Harrison and Woolpert can be satisfactorily explained without upsetting the theory of axonic spread.

Flexner's M. V. strain is, as the name implies, a mixture of strains. With frequent passage it is possible, as Clarke [5] has intimated, to have one of the strains in the mixture separate itself out and become the predominant and passage strain in a particular laboratory. This might well be one of the weaker strains of the mixture. This, of course, could not account for our experience, since our strain II became more potent with passage.

CONCLUSIONS

1. There may be a quantitative difference in virulence between descendants of the same strain of poliomyelitis virus carried by different laboratories.

2. A difference in quantitative virulence in strains of poliomyelitis virus would easily explain negative results following their injection into peripheral nerves.

3. This difference could possibly arise from the fact that we did not transfer our virus frequently enough and that glycerin had some attenuating effect.

4. The results of our present experiments support the theory of axonic spread of poliomyelitis virus.

5. Clarke, P. F.: Personal communication to the authors.

TOXOPLASMIC ENCEPHALOMYELITIS

V. FURTHER OBSERVATIONS OF INFANTILE TOXOPLASMOSIS; INTRAUTERINE INCEPTION OF THE DISEASE; VISCERAL MANIFESTATIONS

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In 1936 and 1938, 2 infants that died at the Babies Hospital within a month of their birth were found at autopsy to have an unusual type of encephalomyelitis. The disseminated inflammation was characterized by necrosis and miliary granulomas and was associated with focal chorioretinitis. It was evidently due to a specific protozoon, the identity of which was difficult to determine (Wolf and Cowen, 1937 [1]). The morphology of the causative micro-organism and the nature of the pathologic process induced by it soon suggested that the parasite was a Toxoplasma (Wolf and Cowen, 1938 [2]). This was confirmed by a study of the biologic characteristics of the micro-organism isolated in the second case (Wolf, Cowen and Paige, 1939, 1940 [3]). A previously recorded instance of retinal infection in an infant (Jankû, 1923 [4]) and

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2. Wolf, A., and Cowen, D.: Granulomatous Encephalomyelitis Due to a Protozoan (Toxoplasma or Encephalitozoon): II. Identification of a Case from the Literature, Bull. Neurol. Inst. New York **7**:266-290, 1938.

3. Wolf, A.; Cowen, D., and Paige, B.: (*a*) Human Toxoplasmosis: Occurrence in Infants as an Encephalomyelitis; Verification by Transmission to Animals, Science **89**:226-227, 1939; (*b*) Toxoplasmic Encephalomyelitis: III. A New Case of Granulomatous Encephalomyelitis Due to a Protozoon, Am. J. Path. **15**:657-694, 1939; (*c*) Toxoplasmic Encephalomyelitis: IV. Experimental Transmission of the Infection to Animals from a Human Infant, J. Exper. Med. **71**:187-214, 1940.

4. Jankû, J.: Parasites in Coloboma of Macula, Časop. lék. česk. **62**:1021-1027, 1054-1059, 1081-1085, 1111-1115 and 1138-1143, 1923.

an incompletely described case of congenital encephalomyelitis, myocarditis and myositis (Torres, 1927 [5]) had been reported as being due to a protozoan parasite. Jankû did not identify the micro-organism in his case beyond suggesting that it was a Sporozoon. Torres gave an excellent description of the parasite in his case. Weighing Toxoplasma against Encephalitozoon, he decided in favor of the latter. Levaditi (1928 [6]), in reviewing these 2 cases, expressed the opinion that they were instances of human toxoplasmosis. As pointed out elsewhere,[1] the evidence, although incomplete, indicated that the cases of Jankû and Torres were instances of the same disease process as that described by us. The positive identification of the parasite as a Toxoplasma, first made possible by the transmission of the infection to animals from the second of our cases,[3a, c] permitted the conclusion that all 4 cases were instances of human toxoplasmosis, or more precisely of infantile toxoplasmic encephalomyelitis. A further instance of this disease was added when it became possible to identify Toxoplasma in sections of the brain in a case which had previously been described by Richter as an instance of meningoencephalomyelitis neonatorum of unknown etiology.[7] Subsequently, toxoplasmosis was described as a generalized parasitic infestation (Pinkerton and Weinman, 1940 [8]) and a predominantly pulmonary infection (Pinkerton and Henderson, 1941 [9]) in adults and as an acute encephalitis in older children (Sabin, 1941 [10]). In at least 2 of these cases it was again possible to verify the nature of the organism by transmission of the infection to animals. The

5. Magarinos Torres, C.: Sur une nouvelle maladie de l'homme, caracterisée par la présence d'un parasite intracellulaire, très proche du Toxoplasma et de l'Encéphalitozoon, dans le tissu musculaire cardiaque, les muscles du squelette, le tissu cellulaire sous-cutané et le tissu nerveux, Compt. rend. Soc. de biol. **97**:1778-1781, 1928; Morphologie d'un nouveau parasite de l'homme, Encephalitozoon chagasi, n. sp., observé dans un cas de méningo-encéphalo-myélite, congénitale avec myosite et myocardite, ibid. **97**:1787-1790, 1928; Affinités de l'Encéphalitozoon chagasi, agent étiologique d'une méningo-encéphalo-myélite congénitale avec myocardite et myosite chez l'homme, ibid. **97**:1797-1799, 1927.

6. Levaditi, C.: Au sujet de certaines protozooses héréditaires humaines à localisation oculaire et nerveuse, Compt. rend. Soc. de biol. **98**:297-299, 1928.

7. (*a*) Wolf and Cowen.[2] (*b*) Richter, R.: Meningo-Encephalomyelitis Neonatorum: Anatomic Report of a Case, Arch. Neurol. & Psychiat. **36**:1085-1100 (Nov.) 1936.

8. Pinkerton, H., and Weinman, D.: Toxoplasma Infection in Man, Arch. Path. **30**:374-392 (July) 1940.

9. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814 (March 1) 1941.

10. Sabin, A.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**:801-807, (March 1) 1941.

clinical manifestations and pathologic changes in these cases differed from those of infantile toxoplasmosis. The encephalitic lesions described in 1 older child were few and mild as compared with the severe changes in infantile toxoplasmic encephalomyelitis. In the adults the lungs were chiefly involved. Other organs were affected to a lesser degree; the brain showed the fewest lesions.

Toxoplasma is a protozoan parasite of uncertain classification, characterized by an affinity for many tissues but especially for the central nervous system, by widespread geographic distribution and by pathogenicity for a wide variety of hosts, especially rodents and birds. In smears, the parasites appear as well outlined, crescentic or curved masses of protoplasm 4 to 6 microns in length and 2 to 3 microns in width. The extremities are usually pointed, although one end may be rounded. In histologic sections of fixed tissue or under pressure, ovoid, rounded or fusiform types are more commonly seen, 2 to 3 microns in length and 1.5 to 2 microns in width. Each parasite contains a rounded chromatin mass situated centrally or nearer the blunter extremity. In addition to the single parasites, larger rounded masses of what appear to be aggregations of closely approximated parasites are seen. Such masses are sometimes referred to as cysts, although it is uncertain whether they possess a true cyst wall.

It is the purpose of the present paper to describe 3 additional cases of infantile toxoplasmic encephalomyelitis recently encountered at the Sloane Hospital for Women and at the Babies Hospital in New York and to record the finding of Toxoplasma in sections of the brain from a previously reported case of chronic acquired hydrocephalus in which there was a meningoencephalitis of undetermined cause (de Lange, 1929[11]).

REPORT OF CASES

CASE 3.[12]—L. M., a white girl, was born at Sloane Hospital on July 7, 1939.

Family History.—The father was a Scottish-born traveling auditor, aged 32, who had lived in the city of New York since he was 2 years old. He had always been in good health. The mother was born in New York and had spent her life in a relatively suburban locality of that city. Except for a mild attack of whooping cough at the age of 4 years, she had had no illnesses. During childhood she had made one trip to Scotland. Both parents had traveled extensively in the United States, principally in the midwestern and western states, but had never been farther south than Maryland in the East. In the summer of 1938, the

11. (*a*) de Lange, C.: Klinsiche und pathologisch-anatomische Mitteilungen über Hydrocephalus chronicus congenitus und acquisitus, Ztschr. f. d. ges. Neurol. u. Psychiat. **120**:433-500, 1929. (*b*) Wolf, A., and Cowen, D.: Toxoplasmic Encephalomyelitis, in Blumer, G.: Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1940, supp.

12. For case 1, see footnotes 1 and 2. For case 2, see footnote 3 b.

mother had spent several weeks in Newfoundland, and in 1939, during her pregnancy, had been in Baltimore for a short time. Contacts with animals which might possibly harbor Toxoplasma were limited to a pet dog kept by the father for many years. This animal had shown no evidence of disease. Cats, canaries, rabbits and other animals had never been kept as pets, nor had there been any obvious infestation of the home by mice or rats.

The mother was 32 years old, and this was her first pregnancy. Her reaction to the Kline test was negative. On June 7, 1939, in the thirty-second week of gestation, she was admitted to the hospital because of premature rupture of the membranes. There was moderate leakage of amniotic fluid during the twelve days she was under observation. At the end of that time she was discharged, since labor did not begin and since there had been no elevation of temperature. On June 27, 1939, roentgenograms gave evidence of uterine fibromyomas displacing the fetal head. The presence of uterine tumors was confirmed by physical examination. After labor of forty hours' duration with artificial rupture of the membranes and episiotomy, the infant was delivered on July 7, 1939, in the thirty-seventh week of gestation. There is no record that the placenta was abnormal, and no histologic examination of it was made.

Personal History.—At birth, the child measured 47 cm. in length and weighed 2,300 grams. Respiration was normal. Examination two hours after birth showed a slightly premature infant with fairly good color and cry. There was marked molding of the head, all the cranial sutures were widely separated and a large cephalhematoma was present posteriorly. There was a paralysis of the right side of the face. On the right cheek, arms and legs were scattered, apparently old ecchymoses. The tip of the spleen was palpated 1 cm. below the left costal margin, and the lower edge of the liver lay 2 cm. below the right costal margin.

On the day after birth, the circumference of the head was 35 cm. It increased rapidly in size, reaching a circumference of 38.3 cm. on the twelfth day and of 40.7 cm. on the seventeenth day; this amounted to approximately five times the normal growth rate for the period. During this time the veins of the scalp became increasingly prominent, the anterior fontanel became more tense and the infant's cry developed a piercing quality.

Roentgenographic examination on the sixth day of life showed the skull to be large for the age, the cranial bones widely separated and the calvarium thinner and less dense than is usual at this age. Although no intracranial calcification was noted at this time, reexamination of the films post mortem, when the nature of the disease became known, revealed small shadows of calcium density in the anterior parietal region just behind the coronal suture and approximately midway between the vertex and the floor of the orbit. At the age of 13 days, roentgen examination of the skull disclosed, in addition to the changes usually seen in hydrocephalus, deposits of calcium in the brain (fig. 2*A*), apparently in the frontal and occipital lobes. Examination of the eyes on the twelfth day showed both eyes to be smaller than normal, the corneas measuring approximately 7 to 8 mm. in diameter. The pupils were fixed to light and measured 2.5 mm. in diameter. Some large vessels were visible in the irises, and in both eyes "membranous masses," apparently vascularized and obscuring the fundi, were seen posterior to the lenses. Pinkish reflexes were obtained through the membranes in the vitreous. A diagnosis of congenital microphthamos was made, and the possibility of persistent tunica vasculosa lentis, retinoblastoma or detachment of the retina was suggested. There were nystagmoid movements of the eyes and tremors and

twitching movements of the extremities. The deep tendon reflexes were hyperactive, and there was a transient patellar clonus. The upper respiratory tract chest, abdomen and genitalia were normal.

Laboratory Findings.—Blood Count: When the child was 17 days of age the hemoglobin content was 14.1 Gm. per hundred cubic centimeters, and the erythrocytes numbered 3,700,000 and the leukocytes 5,200 per cubic millimeter. The differential count showed neutrophils 13 per cent, lymphocytes 71 per cent, monocytes 7 per cent, eosinophils 8 per cent, and basophils 1 per cent. At the age of 28 days a leukocyte count showed white blood cells 7,100 per cubic millimeter, with neutrophils 31 per cent, lymphocytes 55 per cent, monocytes 3 per

Fig. 1.—Cross section of cerebral hemisphere, showing internal hydrocephalus, ependymitis, and oval, sharply demarcated lesion in globus pallidus. Insert in lower right corner shows membranous mass in vitreous of eye. Case 3.

cent and eosinophils 11 per cent. At the age of 48 days the hemoglobin content was 9 Gm. per hundred cubic centimeters and the erythrocytes numbered 2,700,000 and the leukocytes 15,800 per cubic millimeter, with neutrophils 44 per cent, lymphocytes 46 per cent, monocytes 8 per cent, eosinophils 1 per cent and basophils 1 per cent.

Kline Test of Blood: The reaction to a Kline test made when the child was 31 days of age was negative.

Cerebrospinal Fluid: When the child was 20 days of age, lumbar puncture yielded clear, faintly xanthochromic fluid under normal pressure. The Pandy reaction was 4 plus, the total protein content 177 mg. per hundred cubic cen-

timeters, the sugar 43 mg. per hundred cubic centimeters and the chloride content (as sodium chloride) 616 mg. per hundred cubic centimeters. A cell count showed 180 red blood cells and 5 white blood cells per cubic millimeter. Ventricular puncture yielded xanthochromic fluid under increased pressure. The total protein content was 323 mg. per hundred cubic centimeters, the sugar content 23 mg. and the chloride content 653 mg. A cell count showed 480 red blood cells, 7 lymphocytes and 1 polymorphonuclear cell per cubic millimeter. No microorganisms were seen in smears made from the spinal and ventricular fluid, and no bacteria were cultivated.

Dye Test and Ventriculography: When the infant was 22 days of age, a dye test was made and ventriculograms were taken. Two cubic centimeters of a solution of phenolsulfonphthalein was introduced into the lateral ventricle. No dye was recovered on lumbar puncture one-half hour later. Pink fluid was removed from the lateral ventricles three days later and replaced by air. Ventriculograms showed enlargement of both ventricles and considerable cerebral hypoplasia. Repetition of the dye test and ventriculography at the age of 38 days again demonstrated a marked noncommunicating hydrocephalus and cerebral atrophy. The third and fourth ventricles and aqueduct were not visualized. The areas of calcification previously seen were thought to be located in the caudate nuclei.

Roentgenograms of the long bones showed no abnormalities.

Course.—Except for a mild transient rise in temperature, there was no adverse reaction to the dye and air tests. Bilateral enophthalmos was noted, and the right palpebral fissure was larger than the left. There was apparent limitation of left lateral gaze, and irregular nystagmoid jerks were noted on right lateral gaze. The head continued to increase in size and eventually reached a circumference of 48.5 cm., with widely separated sutures. During the last two weeks of the illness, twitching movements of the lower extremities were observed and on some days the infant was drowsy. The extremities were cold and clammy. Trismus made feeding a difficult problem, and in the last week there were several convulsive seizures. The body temperature during much of the illness varied between 97 and 99 F. During the last ten days, it fell several times to or below 96 F. and on the day of death to 94.6 F. In the last twenty-four hours respiration was shallow, labored and irregular. Death occurred on Sept. 9, 1939, when the child was 9 weeks old. The final diagnosis was obstructive hydrocephalus. The lesions in the eyes were thought possibly to be retinoblastoma.

Gross Observations at Autopsy.—A complete autopsy was performed eleven hours after death. The body measured 53 cm. in length and weighed 2,860 Gm. The head was much enlarged, its circumference being 48.5 cm. The anterior fontanel measured 13 cm. in width, and the posterior, 9 cm. The sutures gaped widely, and the veins of the scalp were prominent. Both eyes were smaller than normal.

The cerebral hemispheres were symmetric but were greatly enlarged. The gyral pattern was normal, but the gyri were distinctly flattened and the sulci narrowed. The posterior two thirds of each hemisphere exhibited greater flattening than the frontal regions. The leptomeninges showed discrete, focal, pale lemon yellow or gray areas of discoloration which varied in size from tiny specks to lesions 1 cm. in diameter. They were spotted or lacy in appearance and occurred over the convexity and less often on the medial surfaces of the hemispheres. The remainder of the leptomeninges was thin and translucent. The cerebral parenchyma was friable. The floor of the third ventricle was thin and translucent. There was herniation through the incisura of the tentorium of the

medial portion of the left temporal lobe. A part of the herniated tissue had become adherent to the dorsal surface of the vermis of the cerebellum, indenting it considerably. The tectum of the midbrain was compressed between this herniation and a lesser one of the right hippocampus through the incisura. The cerebellum was flattened dorsoventrally, and the pons and medulla were somewhat flattened on their ventral surfaces. The arteries at the base of the brain were of small caliber and their walls were delicate.

On section of the cerebrum, the lateral ventricles were found to be enormously dilated (fig. 1). The dilatation was relatively greater in the posterior portions of the ventricles. The width of the centrum ovale, the subcortical white matter and

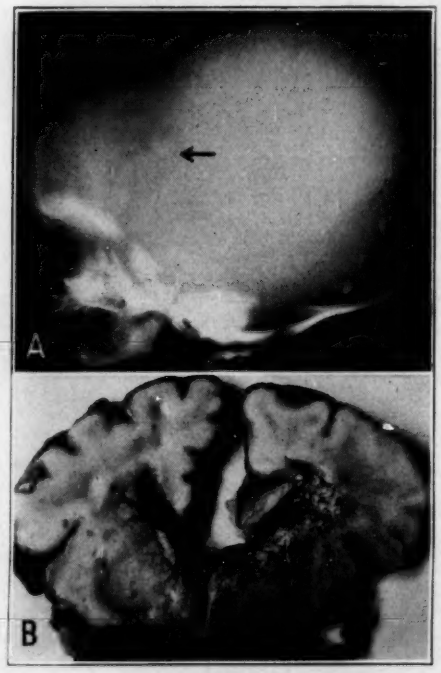

Fig. 2.—*A*. Roentgenogram of skull; arrow indicates calcification in cerebrum; case 3. *B*. Cross section of cerebrum; areas of periventricular necrosis and large necrotizing lesions in basal ganglions and thalamus; case 4.

the cortex was markedly reduced, being less than a millimeter in some places, so that the tissue was translucent. This was most evident in the posterior portions of the parietal lobes and in the occipital lobes, particularly on their lateral aspects. The cortex in the frontal lobes was fairly well preserved, the ventricular dilatation causing a narrowing of the white matter but leaving the gray matter of normal width. The temporal lobes showed marked thinning of the parenchyma, affecting the white matter more than the gray. This thinning was intermediate in degree between that in the occipital and that in the frontal regions. The ependymal surface of the lateral ventricles was granular, roughened and pitted and was covered by friable grayish yellow necrotic material which obscured

the normal landmarks. Part of the irregularity of the ventricular walls was due to a band of necrotic periventricular tissue varying from 1 to 4 mm. in width. This was pale gray and was bounded externally by a translucent grayish white border. The choroid plexuses of the lateral ventricles were compressed and reduced to small smooth nodules of firm pinkish tissue markedly adherent to the floor of the ventricle. The interventricular foramens were completely occluded by adhesions between the flattened, attenuated fornices and the anterior poles of the thalami. The septum pellucidum was thin and had a central fenestration through which the lateral ventricles intercommunicated. The corpus callosum was greatly flattened. The third ventricle was normal in size. The ependymal surface was smooth and glistening. The choroid plexus of this ventricle was pale and delicate and could be traced forward as far as the occluded interventricular foramens, which appeared as shallow depressions.

Occasional yellowish white punctate lesions about 1 mm. in diameter were found in the centrum ovale of the left frontal lobe. The basal ganglions showed scattered punctate yellowish and yellowish white areas 0.5 to 1 mm. in diameter. Some yellowish brown areas 1 to 2 mm. in diameter were present on the posterior surface of the thalamus. The posterior two thirds of the head of the right caudate nucleus was granular, yellowish brown and soft and contained numerous cysts, the largest of which was 3 mm. in diameter. An oval lesion measuring 1.5 by 0.5 cm. was present in the left globus pallidus (fig. 1). This was grayish and translucent centrally and had a yellowish marginal band 0.5 mm. in width. A periventricular band of necrosis, similar to that seen elsewhere in the ventricular walls, was present on the juxtaventricular surfaces of the basal ganglions. This varied from 2 to 3 mm. in width, and in it there were some irregular white streaks and dots which were gritty. A similar irregular mass of gritty material was present in a grayish, translucent zone, measuring 5 by 3 by 3 mm., in the subthalamic region.

Section of the cerebellum revealed no abnormalities. The aqueduct of Sylvius was compressed from side to side in its upper third but was patent throughout. The periaqueductal parenchyma appeared normal. There were no gross lesions in the midbrain, pons or medulla. The fourth ventricle was normal in size and shape, and its ependymal lining was smooth and shiny.

The spinal dura and leptomeninges appeared normal. The cervical enlargement was somewhat swollen. There was slight constriction of approximately one segment in the midthoracic region, which was discolored a faint brownish yellow. Similar discoloration of the twelfth thoracic segment was noted. On section of the spinal cord the outlines of the posterior horns and the left anterior horn were found to be obscured in the region of the cervical enlargement. This was due to a grayish and glassy appearance of these horns and of the posterior columns and the dorsal portions of the lateral columns. Occasional tiny cysts were present in this tissue. Sections through many levels of the thoracic cord revealed scattered sharply marginated patches of a grayish glistening tissue, which frequently had a yellowish or cream-colored center. These were most frequent in the posterior and lateral columns. The lumbosacral cord was normal except for an occasional yellowish nodule.

In the posterior portions of both eyes the retina was detached from the choroid and masses of gray translucent tissue, 7 by 7 mm. and 9 by 3 mm., projected forward into the vitreous almost to the lenses (fig. 1).

Microscopic Observations at Autopsy.—Brain and Spinal Cord: Large areas of necrosis and inflammation were found in the cerebral cortex, the subcortical

white matter, the centrum ovale, the periventricular tissues of the lateral ventricles, the striatum, the pallidum, the thalamus, the lower part of the medulla and the cervical and thoracic portions of the spinal cord. The structures involved had lost their architectural markings, owing to destruction of neural and neuroglial elements. The space was occupied by amorphous debris and varying numbers of polymorphonuclear leukocytes and lipid-laden phagocytes. Lymphoytes, plasma cells, large mononuclear cells and in some places varying numbers of eosinophils, some of which were eosinophilic myelocytes, were present perivascularly and were diffusely scattered, chiefly at the margins of the degenerated zones. Here capillaries had multiplied, had undergone endothelial hyperplasia and in some lesions had given rise to fibroblasts. In this marginal tissue of the necrotic zone and beyond it, persisting neural and neuroglial cells were found in various stages of degeneration. There were associated edema, congestion, astrocytosis and activation of the

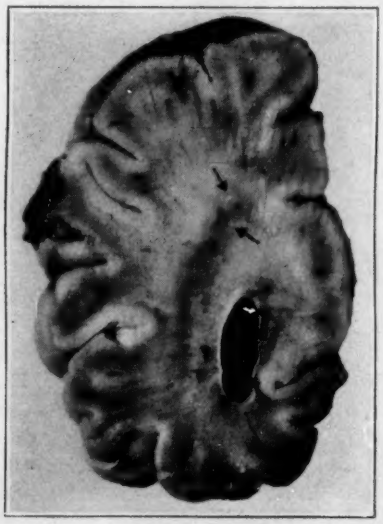

Fig. 3.—Cross section of posterior portion of cerebral hemisphere. Note miliary lesions in centrum ovale, indicated by arrows. Case 5.

microglia cells. Many of the astrocytes had undergone clasmatodendrosis, and the oligodendroglia cells were swollen. In the head of the right caudate nucleus, cysts had developed within the necrotic zones. Some of the necrotizing lesions, particularly those in each globus pallidus and putamen and to a slightly lesser degree those in the cerebral cortex of the frontal and occipital lobes and in the island of Reil, were extensively clacified (fig. 6 *D*). Astrocytosis was more intense in these areas. The calcium occurred as coarsely granular, opaque, bluish material or concentric, laminated spherules, in places agglomerated into larger, denser, mulberry-like masses lying in the glial meshwork. Many cells and their processes, chiefly nerve cells, appeared to be encrusted.

Two other types of smaller lesions were often found scattered at the margins of the large necrotizing ones and irregularly disseminated throughout the rest of the gray and white matter of the brain and the spinal cord. The larger of these was imperfectly outlined and marked by vascular mural, perivascular and diffuse

infiltration by lymphocytes, large mononuclear cells and varying numbers of polymorphonuclear leukocytes. There was some loss of neural elements, nerve cells, axons and myelin sheaths, with evidence of degeneration of some of the remaining ones in these areas. Hypertrophied astrocytes and microglia cells, the latter elongated and rodlike and their nuclei at times slender and misshapen, were also present. The capillaries showed endothelial hyperplasia.

The smaller lesions were miliary granulomas (fig. 5 *A*). These were composed of large polygonal or irregular cells with abundant, finely granular, pale eosinophilic cytoplasm and large, light-staining, oval or irregular nuclei containing a small amount of finely granular chromatin with a few coarser granules (fig. 5 *B*). These seemed to be distinctly related to the plump endothelial cells of hyperplastic capillaries.

As previously mentioned, there was a band of periventricular necrosis in the walls of the lateral ventricles, where the ventricular surfaces were denuded of ependyma. The changes in the ventricular walls were similar to those in the other necrotizing lesions except for a greater proliferation of capillaries and fibroblasts. On the surface of the ventricles was an exudate composed of polymorphonuclear leukocytes and fibrin. Small numbers of lymphocytes, large mononuclear cells and eosinophilic amorphous debris were also present. Ependymal granulations were encountered in the non-necrotic areas of the walls of the ventricular system. Through their fusion, in part, stenosis of the interventricular foramens and, to a lesser degree, of the caudal portion of the aqueduct of Sylvius had occurred (fig. 6 *C*).

The leptomeninges overlying parenchymal lesions were focally infiltrated by lymphocytes (fig. 5 *A*), plasma cells, large mononuclear cells and occasional eosinophils. Where the parenchymal lesion was necrotic there were often polymorphonuclear leukocytes in the corrsepondingly more heavy exudate, and the line of demarcation between parenchyma and pia-arachnoid was frequently blurred. In these areas there were also an increase in and hypertrophy of pial and arachnoid cells and endothelial hyperplasia of pial capillaries.

The choroid papillae were congested but not otherwise abnormal. Intense infiltration with the formation of granulation tissue, partially organized, in the tela choroidea at the anterior extremities of the lateral and third ventricles contributed to the stenosis of the interventricular foramens.

Eyes: Chorioretinal lesions were present in each eye. The changes in the retina were essentially of the same necrotizing and inflammatory type as those noted in the brain. There were present edema, congestion, degeneration and disappearance of neural elements, dislocation of portions of the nuclear and hypertrophied pigmented layers (fig. 7 *B*), moderate perivascular and diffuse infiltration by lymphocytes and plasma cells, varying degrees of astrocytosis and endothelial hyperplasia of capillaries and outgrowth of granulation tissue into the vitreous. This outgrowth of granulation tissue was greater in degree than in the previous cases and formed the large masses observed ophthalmoscopically. The choroid was moderately infiltrated and congested. The sclera appeared normal.

Toxoplasmas were present in most of the lesions (fig. 12 *B*). They were predominantly oval, though piriform, round and fusiform elements were also encountered. They averaged approximately 2.4 by 1.4 microns in size and varied from 1.8 to 3.1 microns in length and from 1.1 to 1.9 microns in width. At one pole or one side of the organism was a spherical or oval chromatin body, often having a lighter-staining center and bordered by a halo of less densely staining cytoplasm. These organisms

were in places agglomerated into dense clusters which have been described as cysts (fig. 12 *A*). These cysts varied in size from 7.4 by 9.4 microns to 10.8 by 12.3 microns.

The individual toxoplasmas and clusters were found both intracellularly and extracellularly. The intracellular ones were most often present in large mononuclear cells. Toxoplasmas were most abundant in the necrotizing lesions and least in the leptomeninges.

In addition to the toxoplasmas, alpha streptococci were present in the ventricular exudate and were evidently secondary and terminal invaders. They undoubtedly gave rise to the acute ependymitis. They were absent in the leptomeningeal exudate and in the parenchymal lesions.

Other Organs: No gross abnormalities of the other organs were found. Histologically, extramedullary hemopoiesis was noted in the liver and spleen. Toxoplasmas and toxoplasmic lesions were carefully sought for, but none was found.

Fig. 4.—Large areas of necrosis and caseation in thalamus, basal ganglions and periventricular region. Internal hydrocephalus. Reproduced by courtesy of Dr. de Lange.

Experimental Transmission of the Infection to Animals.—Several small pieces of cerebral cortex and white matter containing gross lesions (focal areas of yellowish discoloration) were removed from the brain under aseptic precautions at autopsy, eleven hours after death. The tissue was ground in a sterile mortar, suspended in physiologic solution of sodium chloride and inoculated into a rabbit (0.2 cc. intracerebrally) and 3 mice (0.02 cc. intracerebrally and 0.2 cc. intraperitoneally). Eight mice were similarly inoculated with a suspension of splenic tissue.

Of the 3 mice inoculated with cerebral tissue, 1 died on the fourth day. A compact hemorrhage (1 by 4 mm.) at the site of inoculation in the left cerebral hemisphere was noted. Histologically, there was a mild acute inflammatory reaction about this lesion and one cluster of toxoplasmas was identified. Culture of this brain tissue yielded alpha streptococci; that of the peritoneum, no growth. Inoculation of brain tissue from this animal into three mice was without effect, the

animals remaining well and showing no lesions in their brains when examined after nine months.

The other 2 mice inoculated with cerebral tissue of infant L. M. died in eleven days of meningoencephalitis and toxoplasmas in the lesions. Focal necrotizing inflammatory lesions were present in the livers of these mice, but no toxoplasmas were identified in this organ. The other organs were normal. Brain tissue from one of these mice subinoculated into 3 mice and a rabbit produced a fatal toxoplasmosis, as did a suspension of liver, spleen and lung when subinoculated into a single mouse. Cultures of these tissue suspensions were bacteriologically sterile. Subinoculation of brain tissue from the other mouse was unsuccessful. The rabbit inoculated intracerebrally with brain tissue from infant L. M. remained healthy, and histologic examination of its brain after twenty-one months revealed no toxoplasmas or lesions of toxoplasmosis. The 8 mice inoculated with splenic tissue also remained healthy, and no lesions or parasites were found in their brains when they were examined nine months later. These animals were from the same stock as those succumbing to the inoculation of brain tissue from infant L. M. and serve as controls to exclude the possibility of chance activation of a latent spontaneous infection in the animals which developed toxoplasmic encephalitis.

The strain of Toxoplasma derived from this patient (L. M. strain) has been maintained by serial passage in mice and rabbits to date. The morphology and pathogenicity of the parasite, the course of the infection and the pathologic lesions in experimentally infected animals are in all respects similar to those described in detail in connection with a previously isolated human strain of Toxoplasma (BD strain) from a case of infantile toxoplasmic encephalomyelitis.[3a,c] The LM strain is also pathogenic for guinea pigs.

Cross Immunity: Rabbits and mice proved by repeated intracerebral inoculation of infected brain tissue suspensions to be immune to the LM strain have been found to be completely resistant when reinoculated intracerebrally with the previously studied human (BD) strain. Conversely, animals known to be immune to the BD strain are resistant when reinoculated intracerebrally with the otherwise lethal LM strain. There would appear to be complete cross immunity, therefore, between these two human strains of Toxoplasma.

Summary of Case.—A white female infant, slightly premature, gave evidence of progressively increasing hydrocephalus which had been noted two hours after birth. Roentgenographic evidence of cerebral calcification was present on the sixth day. During the second and third weeks of life, microphthalmos and membranous masses in the vitreous of each eye were noted. The spinal fluid showed xanthochromia and a high protein content. There were tremors and convulsions late in the course. The infant died at 9 weeks of age. Necropsy revealed a diffuse necrotizing encephalomyelitis in which miliary granulomas and extensive calcification were conspicuous. Marked internal hydrocephalus was due to occlusion of the interventricular foramens and stenosis of the aqueduct of Sylvius. Chorioretinitis was present in each eye, with an outgrowth of partially organized granulation tissue into each vitreous. Toxoplasmas were present in the lesions of the brain, spinal cord and eyes, and mice inoculated with cerebral tissue acquired a typical murine toxoplasmosis. No toxoplasmas were found in any of the other organs.

There was a terminal superimposed acute ependymitis due to alpha-streptococci.

CASE 4.—The second case of infantile toxoplasmic encephalomyelitis reported here is of great interest because it establishes beyond question that the infantile form of the infection may be prenatal in origin.

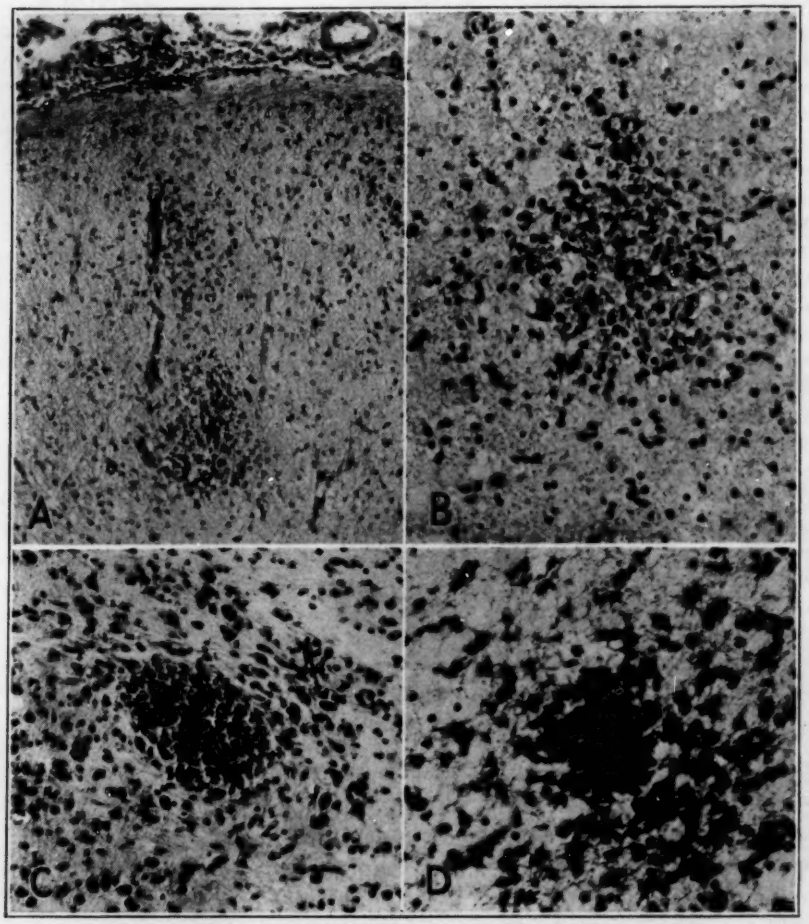

Fig. 5.—*A*. Granulomas in cerebral cortex; lymphocytic leptomeningitis; case 3; hematoxylin-eosin stain; × 110. *B*. Granuloma in cortical white matter; case 3; hematoxylin-eosin stain; × 230. *C*. Granuloma in pons; case 5; hematoxylin-eosin stain. *D*. Granuloma in centrum ovale of cerebrum; de Lange's infant; hematoxylin-eosin stain.

Baby R., a Negro boy, was delivered dead at Sloane Hospital on April 18, 1940.

Family History: The parents were born in the British West Indies. The father, 42 years old, was a cook who had been in the city of New York for

twenty-four years. He had apparently always been in good health except for an episode twenty-four years previously, when he was ill in bed for three months. At that time he had abdominal pains, "swelling" of the abdomen, vomiting and fever, followed by constipation, generalized weakness and loss of weight. The Wassermann reaction of his blood was repeatedly negative. The mother, 35 years old, a domestic worker, had been in New York for eleven years, except for a six month period, three years prior to her pregnancy, when she had visited Jamaica. Her past medical history had been without incident except for a myomectomy and appendectomy six years previously. The family had never had any pets. The home was in a poor residential district and had been mildly infested by mice.

This was the mother's first pregnancy. The Wassermann reaction of her blood was negative. The greater portion of the pregnancy was normal, but at the end of the seventh month she began to have slight vaginal bleeding, which soon ceased. Examination at this time revealed no abnormalities. Roentgenograms of the pelvis showed a possible deficiency in the calcification of the fetal skeleton; the suture lines of the fetal skull were not well defined, and the possibility was raised of a mild internal hydrocephalus. At the beginning of the ninth month, on April 10, 1940, the membranes ruptured spontaneously and the patient was admitted to the hospital. A pelvic roentgenogram showed the fetus to be at or near full term development, and the size of the skull was considered to be normal at this time. There was a continued leakage of amniotic fluid all week, and labor began on April 18, 1940, approximately two weeks before the expected date. The mother's temperature, which had previously been normal, was now found to be 101.4 F. The fetal heart had been heard on numerous occasions and was audible up to the time of delivery. Pelvic examination shortly before delivery revealed that the fetal skull bones were thin and movable, one on the other, with crepitation, and that the sutures were wide and the posterior fontanel large and bulging. A diagnosis of internal hydrocephalus was made. In order to deliver the child, the posterior fontanel was perforated and the child extracted with the aid of a cranioclast. On puncture of the fontanel approximately 200 cc. of bloody cerebrospinal fluid escaped. The placenta did not separate readily and had to be delivered manually. As it came away, a papyraceous fetus, 20 cm. long and well preserved, was found to be present. The postpartum course was complicated by a vaginal discharge which contained hemolytic streptococci. There were tenderness, distention and rigidity of the lower part of the abdomen and a mild fever. Sulfanilamide was given, and the vaginal cultures became negative at the end of the second postpartum week. A bilateral phlebitis in the lower extremities supervened and occasioned a persistence of the fever, which subsided in the fourth week. The mother was discharged from the hospital at the end of the fifth week. Except for temporary mild backache and swelling of the legs, she remained well and had no complaints when last seen (Oct. 7, 1940).

Gross Observations at Autopsy.—A complete autopsy was performed on the infant thirty-five hours after delivery. The body was that of a full term infant, measuring 52 cm. in length and weighing 2,610 Gm. The head had been collapsed by the craniotomy, and a lacerated wound extended into the cerebrum. The wound was 4 cm. in length and was situated at the junction of the occipital and parietal bones. The sutures were widely separated. There were microphthalmos and enophthalmos of the right eye, and the right pupil was smaller than the left. Meconium oozed from the nose. The body showed no other external abnormalities.

The serous cavities were free from fluid. The larynx, trachea and bronchi contained meconium, and the lungs were unexpanded. The spleen and liver were slightly enlarged. The other organs showed no abnormalities.

Skull: There was marked hemorrhage into the subcutaneous tissues of the scalp. A partial tear was present in the upper leaf of the left side of the tentorium.

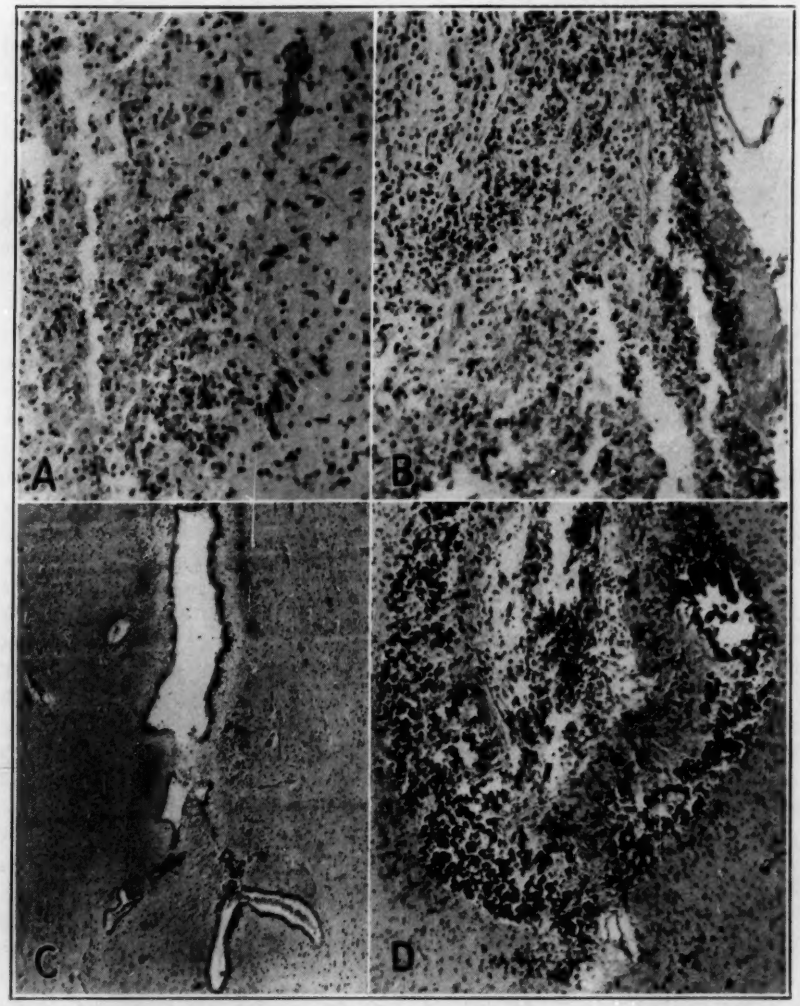

Fig. 6.—*A*. Necrosis and chronic inflammatory reaction in thalamus; case 5; hematoxylin-eosin stain. *B*. Band of necrosis in wall of lateral ventricle; complete loss of ependymal lining; infiltration by lymphocytes and plasma cells; case 4; hematoxylin-eosin stain. *C*. Stenosis of aqueduct of Sylvius due to coalescent ependymal granulations; case 3; hematoxylin-eosin stain; × 60. *D*. Calcification in area of cortical necrosis and inflammation; note persistent chronic inflammatory reaction in leptomeninges; case 3; hematoxylin-eosin stain.

There was a large rent in the posterior portion of the falx. All of these lesions were evidently due to the craniotomy.

Brain: The brain was widely traumatized because of the craniotomy. There were subarachnoid hemorrhages on the inferior surfaces of the temporal lobes. In the untraumatized areas of the cerebrum, the gyral pattern was found to be normal. The gyri were somewhat flattened in the frontal and parietal lobes; they were decidedly flattened in the occipital and temporal lobes. The leptomeninges were thin and translucent throughout, and the leptomeningeal vessels were mildly congested. On section the cortex was found to be considerably reduced in width in the ventral portions of the temporal and occipital lobes, where a thin layer of degenerated parenchyma alone separated the greatly dilated ventricles from the leptomeninges. There was degeneration in the left cingulate gyrus and in the orbital gyri, where the cortex had lost its normal architecture and was soft, yellowish and microcystic and showed no line of demarcation from the underlying white matter. The left transverse gyri of Heschl were grayish, translucent and soft. The cortical changes were frequently continuous with areas of degeneration in the subcortical white matter and the centrum ovale. These appeared yellowish, granular and soft. The lateral ventricles were only slightly dilated in their anterior portions. The atria and the occipital and temporal horns were greatly enlarged. This was due not only to an actual ventricular dilatation but to an extreme necrosis of the ventricular walls involving the centrum ovale, the subcortical white matter and in some places the cortex. This band of periventricular necrosis (fig. 2*B*) extended forward to the anterior parietal and frontal region, where it varied from 1 to 5 mm. in width, being widest in the frontal horns. The band extended into the corpus callosum and the basal ganglia where they bordered the ventricles, and the tissue was yellowish, granular and soft. The corpus callosum was attenuated, soft and studded with yellowish areas which varied in size from pinpoint to several millimeters in diameter. The walls of the lateral ventricles were covered by a thick yellowish white exudate which in places was flaky and stringy. The third ventricle was slightly dilated, and thin flecks of exudate were present on its surface. The periventricular necrosis already described involved the caudate nuclei and the thalami (fig. 2*B*), varying in the depth to which it penetrated. The bodies of the caudate nuclei and the right thalamus were most severely involved. In some places, the entire cross section of the body of the caudate nucleus was destroyed and the necrotic band extended through the entire lateral aspect of the left thalamus to reach the inferior surface of the island of Reil. This area was soft, irregular in outline and yellow, and its center was studded by grayish, slightly sunken, semitranslucent zones. Elsewhere the periventricular necrosis penetrated to a depth of 1 to 6 mm. The hypothalamus in the region of the tuber cinerum and infundibulum was slightly grayish, translucent and soft. Section of the brain stem revealed no parenchymal abnormalities. The aqueduct of Sylvius was compressed from side to side. The cerebellum showed no gross lesions on section. The spinal cord was normal externally and on section.

Microscopic Observations at Autopsy.—Brain and Spinal Cord: Necrotizing and inflammatory lesions similar to those described in the preceding case were seen in the cerebral cortex, the subcortical white matter, the centrum ovale, the periventricular tissues of the lateral and third ventricles, the striatum, the pallidum, the thalamus, and the hypothalamus. These were for the most part quite extensive. Within the lesions the local architecture was disturbed or destroyed by the degeneration and disappearance of many or all of the neural and neuroglial

cells. Where total necrosis occurred, amorphous material lay in a persisting capillary network, in the meshes of which varying numbers of lipid-laden phagocytes and polymorphonuclear leukocytes were seen. A more chronic inflammatory reaction consisting of lymphocytes, plasma cells, eosinophils and large mononuclear cells was present in the outer aspects and at the edges of the necrotic zones;

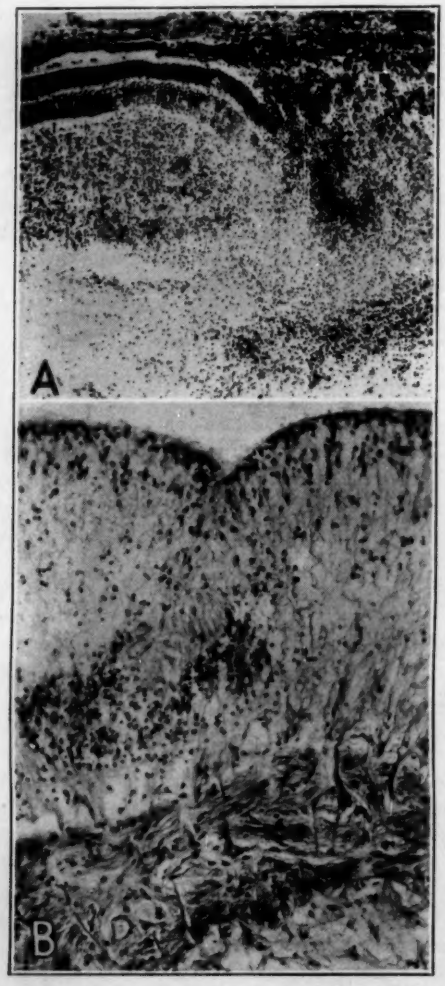

Fig. 7.—*A.* Necrosis of all retinal layers and diffuse chronic inflammation; hypertrophy of pigmented layer and dispersion into inner retinal layers; chronic inflammatory process in choroid; case 4; × 60. *B.* Disorganization of retinal layers and diffuse gliosis; chronic lesion; case 3; × 120.

in some areas it permeated these zones. This inflammation was both perivascular and diffuse and was associated with an endothelial hyperplasia and multiplication of capillaries. At the margins of the lesions the infiltration was predominantly perivascular and was coupled with hypertrophy and multiplication of microglia

cells, astrocytosis, edema, congestion and capillary hyperplasia, with occasional fibroblast formation. Miliary granulomas of the type described in case 3 were seen at the margins of the larger lesions and as isolated nodules in the cortex, the periventricular tissue, the centrum ovale, the hypothalamus, the brain stem and the central white matter of the cerebellum and spinal cord. A number of necrotizing lesions were impregnated with calcium. The calcification was severe in the caudate nuclei, the heaviest deposits being in the left nucleus and in both thalami. It varied from moderate to marked in the cerebral cortex, centrum ovale and periventricular tissue. The calcium occurred as coarse particles, spherules or irregular masses and often seemed to impregnate degenerating nerve cells or their processes.

The periventricular necrosis was similar to the degenerating inflammatory lesions elsewhere and was associated with a complete disappearance of the ependyma (fig. 6 *B*). Wide areas of the walls of the lateral ventricles and to a lesser degree of the third ventricle were involved. Throughout the ventricular system ependymal granulations were frequently found where the ventricular surfaces were intact. In its midportion the aqueduct of Sylvius was considerably narrowed and its lumen reduced in size, owing to coalescent apposing ependymal granulations. There was mild periaqueductal inflammation. In the dorsal portion of the aqueduct, glial tissue completely filled the lumen and was infiltrated by small numbers of lymphocytes and eosinophils. In the central portion of the aqueduct, the coalescent granulations only partially filled the lumen, and their surfaces had become lined with ependyma.

Leptomeningeal infiltration was seen almost exclusively in relation to parenchymal lesions and consisted of focal infiltration by lymphocytes, plasma cells, large mononuclear cells and eosinophils in varying numbers. This infiltration was at times associated with hyperplasia of leptomeningeal cells. Where the underlying parenchymal lesions were most severe, polymorphonuclears and lipid-laden phagocytes were also encountered.

The tufts of the choroid plexus, chiefly in the lateral ventricles, showed occasional infiltration of their connective tissue cores by plasma cells and lymphocytes. They were well preserved. The tela choroidea in many places was heavily infiltrated and hyperplastic. It contained numerous eosinophils and fibroblasts in addition to the other cells.

Large patches of chorioretinitis were seen in each eye (fig. 7 *A*). The retina was considerably swollen, and the changes were fundamentally like those seen in the brain. The necrosis and inflammatory reaction were more recent and more intense than those seen in case 3. These markedly necrotic lesions in the inner layers of the retina were infiltrated by polymorphonuclear leukocytes, lymphocytes, eosinophils and plasma cells, and similar cells mingled with the fibroblasts and capillaries growing out into the vitreous. Dislocation of the degenerated retinal layers with extrusion of portions of the hypertrophied pigmented layer into the inner layers was seen in these lesions, as well as diffuse astrocytosis and capillary hyperplasia. The choroid showed varying degrees of infiltration, chiefly by lymphocytes and plasma cells, predominantly in the choriocapillary layer and in regions adjacent to retinal lesions. The sclera was normal.

Toxoplasmas were present in the great majority of the lesions (fig. 12 *C* and *D*) and were similar in appearance, size, intracellular and extracellular occurrence and distribution to those described in case 3.

Other Organs: In the heart, scattered muscle fibers contained closely packed aggregates of parasites, often without a sharp line of demarcation between organ-

isms and myofibrils. The parasitized fibers were somewhat swollen at the site of infestation, but failed to show necrosis. No degenerative lesions were found in other fibers, and no inflammatory reaction was found in the immediate vicinity of the parasites. However, elsewhere in the interstitial tissue, as well as in the endocardium and epicardium, there were collections of lymphocytes, plasma cells, occasional polymorphonuclear leukocytes, undifferentiated myeloid cells, eosinophilic

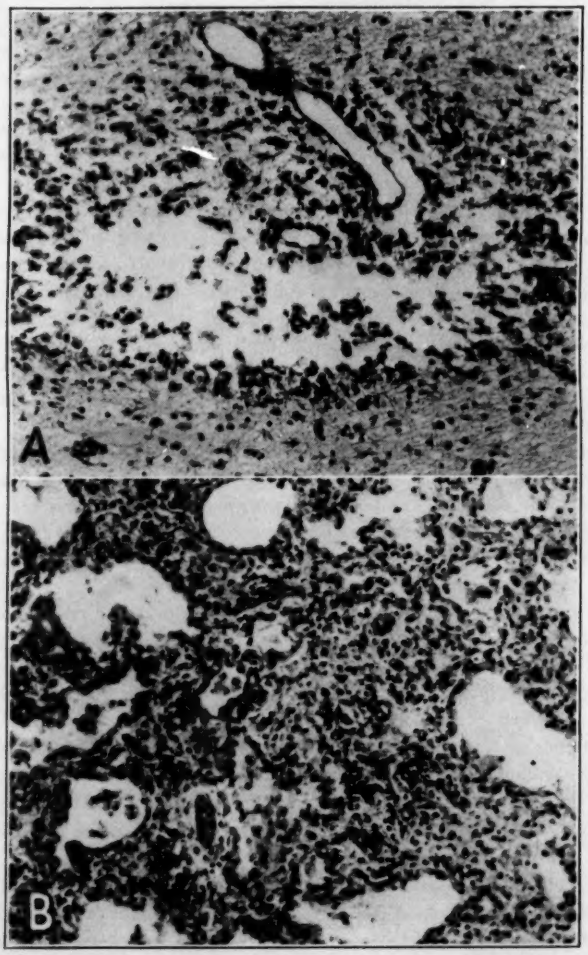

Fig. 8.—*A*. Localized necrotizing lesion in subcortical white matter of cerebrum; numerous lipid-laden phagocytes and some lymphocytes; case 5; hematoxylin-eosin stain. *B*. Interstitial pneumonia; note hypertrophy of alveolar lining cells; case 5; hematoxylin-eosin stain.

myelocytes and eosinophils and occasional erythrocytes. No parasites were found in the areas of inflammation. Occasional pairs of gram-positive cocci were seen in the superficial portions of the endocardium, unrelated in position to the inflammatory foci.

In the lungs many gram-positive cocci, some in pairs and short chains, were present in the alveoli and bronchi, and meconium and epithelial cells from the amniotic fluid had been aspirated. About some of the bronchi and neighboring blood vessels lay small accumulations of myeloid cells, eosinophils and occasional plasma cells. No toxoplasmas were found. The wide fetal cortex of the adrenals was persistent. Scattered throughout the glands were swollen cortical cells, in the cytoplasm of which were many closely packed parasites. Unrelated to the parasitized cells were small focal, necrotizing cellular accumulations in which numerous eosinophils could be identified. No toxoplasmas could be found in the necroses, and no bacteria were demonstrable in them, though occasional gram-positive cocci were found in a capillary near one of the necroses. Occasional striated muscle fibers in the intrinsic muscles of the larynx, a temporal muscle and one of the extra-ocular muscles harbored small to large numbers of parasites. There were focal perivascular infiltrations of lymphocytes, large mononuclear cells and eosinophils in the extraocular muscles. In the liver, spleen, kidneys and testes extramedullary hemopoiesis was active, but no parasites or focal necrotizing lesions were discovered.

Papyraceous Fetus: Gross and microscopic examination of the papyraceous fetus revealed no evidence of toxoplasmosis.

Decidua, Placenta, and Umbilical Cord near Placenta: The amnion was well preserved. In the chorion was an intense polymorphonuclear exudate, and the walls of some of the large veins were infiltrated with leukocytes. On the intimal surface of some of the large veins was a deposition of fibrin in which leukocytes were entangled. The placental villi were normal for the period of gestation. External to those adjoining the chorion was an accumulation of leukocytes which did not invade the villi themselves. Beneath the epithelium of the umbilical cord was a meager infiltration of polymorphonuclear leukocytes, and infrequently there were masses of bacteria. In Wharton's jelly there was a scattering of polymorphonuclear and large mononuclear cells, and the wall of the umbilical vein was infiltrated with a moderate number of similar cells. In the umbilical arteries small cellular infiltrations were also present. Gram-positive cocci were found in the exudate, but no toxoplasmas were present.

Animal Passage.—Attempts to demonstrate the presence of toxoplasmas in the placenta by intracerebral and intraperitoneal inoculation of this tissue into mice were rendered valueless because of the presence of postmortem contaminants. Six mice so inoculated died within twenty-four hours of bacterial infection.

Intracerebral and intraperitoneal inoculation of the mother's whole blood into mice on two occasions and of a suspension of mucoid material removed under sterile precautions from the cervix of the uterus on a third occasion failed to infect mice, the animals remaining healthy during an observation period of six weeks.

Summary of Case.—An infant had given evidence of hydrocephalus in utero, necessitating craniotomy for delivery. The child was born at term, was normally developed except for the enlarged head and was viable up to the time of delivery. On pathologic examination the stillborn child presented an advanced toxoplasmic encephalomyelitis with extensive calcification of the lesions and an associated chorioretinitis. Toxoplasmas were found also in cardiac and striated muscle fibers and in cells of the adrenal cortex. While there was usually no cellular

reaction in the immediate vicinity of the parasitized cells, the focal character of the inflammation and the types of cells found in the inflammatory exudate in the heart and extraocular muscles and also the similarity of the focal inflammatory and necrotizing lesions in the adrenals to the adrenal lesions seen in animals with toxoplasmosis make it highly probable that the disseminated lesions in this case had resulted from the toxoplasmic infection.

CASE 5.—The third case reported here, in which the patient died at 3½ days of age, is of interest because of the widespread involvement

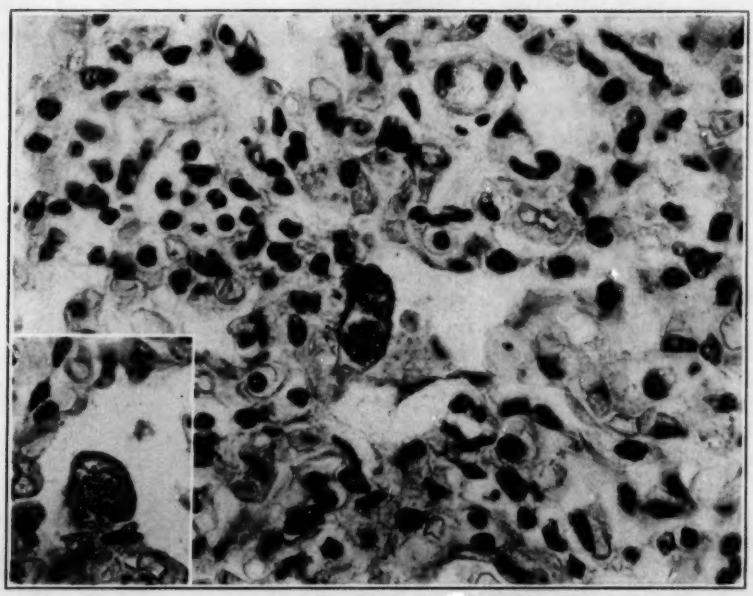

Fig. 9.—Interstitial pneumonia. Note parasitic cyst within alveolar cells and chronic inflammation. Insert: parasitic cyst within alveolar space. Case 5. Hematoxylin-eosin stain.

of organs other than the nervous system and the less advanced state of the neural lesions.

A. M. T., a white girl, was born at the Sloane Hospital on May 31, 1941.

Family History.—The father was 26 years old and had been an elevator operator. He was born in New York and had lived in that city and in its vicinity most of his life. He had always been well. At the age of 20 he had joined the United States Army as an engineer and had been stationed in Panama, where he had had a "fever." There was a history of tick bites without known sequelae.

The mother was born in New York. She had had influenza as a child. Reduction of vision and external strabismus of the left eye were due to a childhood injury. There was no special history of significant contacts with animals. She had not traveled except for summering in the northeastern border states.

She was said to have suffered from "anemia" since puberty. There was a spontaneous abortion of unknown cause after two and one-half months' gestation, in August, 1940. The mother became pregnant again that autumn, and during the first four months of her pregnancy she suffered from severe nausea and vomiting, necessitating a ten day hospitalization. Her blood pressure was not raised. She complained of feeling depressed and weak during most of her pregnancy. The hemoglobin content had been 75 per cent during the eighth month of pregnancy. The Kline test was negative, and the urinalysis gave normal results. Six weeks before the expected date of delivery she was admitted in labor to the Sloane Hospital. Labor lasted nineteen hours, the membranes rupturing spontaneously fifteen minutes before the infant's birth. Episiotomy and low forceps were employed in delivery. The placenta was not noted as being abnormal. She was discharged from the hospital on the fourteenth day, after an uneventful postpartum course.

Personal History.—The infant appeared normal and was in good condition at birth. Her weight was 2,930 Gm., and her length was 48 cm. During the second day of life the respiratory rate rose, and respirations were grunting in character. Breath sounds over the lower lobe of the left lung were slightly exaggerated; the liver was palpable 3 cm. and the spleen 2 cm. below the costal margins; the extremities were cyanotic and the legs were edematous. There was no fever. A blood count on the second day showed hemoglobin 24.5 Gm. (167 per cent), red cells 6,280,000 per cubic millimeter, white cells 22,300 per cubic millimeter, polymorphonuclear leukocytes 61 per cent, lymphocytes 27 per cent, monocytes 8 per cent, eosinophils 4 per cent and 6 nucleated red blood cells per hundred leukocytes.

On the third day the blood count showed hemoglobin 19.2 Gm. (133 per cent), red cells 5,580,000, white blood cells 19,400, polymorphonuclear leukocytes 46 per cent, lymphocytes 40 per cent, monocytes 12 per cent, eosinophils 2 per cent and 7 nucleated red blood cells per hundred leukocytes. Blood culture showed no growth. The temperature rose to 101 F. on this day; the child was cyanotic and restless without oxygen, and respiration was labored. Edema extended to the vulva and death occurred on June 4, when the infant was 3½ days old. The clinical diagnoses considered were congenital heart disease, intracranial injury and sepsis.

A complete autopsy was performed ten hours after death.

Gross Observations at Autopsy.—The body was that of an apparently full term infant. There was moderate edema of the genitalia and lower extremities. The peritoneal cavity contained a slight excess of clear fluid, and there was edema of the lower abdominal wall and of the ligamentous attachments of the liver. The pleural cavities were free of fluid, and both lungs were partially expanded. They were bright pink except for purplish red discoloration of the dependent portions. The cut surfaces were moist. The heart appeared normal. Except for moderate enlargement of the liver and the spleen, the abdominal viscera were not noteworthy. The spleen weighed 21 Gm. and measured 6.4 by 4 by 1.8 cm.

The dura and its sinuses appeared normal, and there was no subdural hemorrhage. The cerebral leptomeninges were somewhat edematous and markedly congested, and there were hemorrhages in them over the right parietal and occipital lobes, the largest being 2 by 3 cm. The spinal leptomeninges were congested. The brain and spinal cord appeared normal externally.

Section of the cerebrum revealed scattered, moderately numerous, circumscribed yellowish or yellowish white lesions in both hemispheres (fig. 3). These occurred in all the cerebral structures, being more numerous in the white matter and somewhat

larger in the gray. They grew more frequent as the occipital poles were approached, and in addition the subcortical and cortical lesions appeared slightly larger in the posterior portions of the cerebrum. In the centrum ovale these punctate areas varied in size from that of a pinpoint to 1 mm. in diameter. The largest of the cortical lesions occurred in the left inferior parietal lobule, one in the cortex measuring 4 mm. in diameter and one in the subcortical white matter measuring

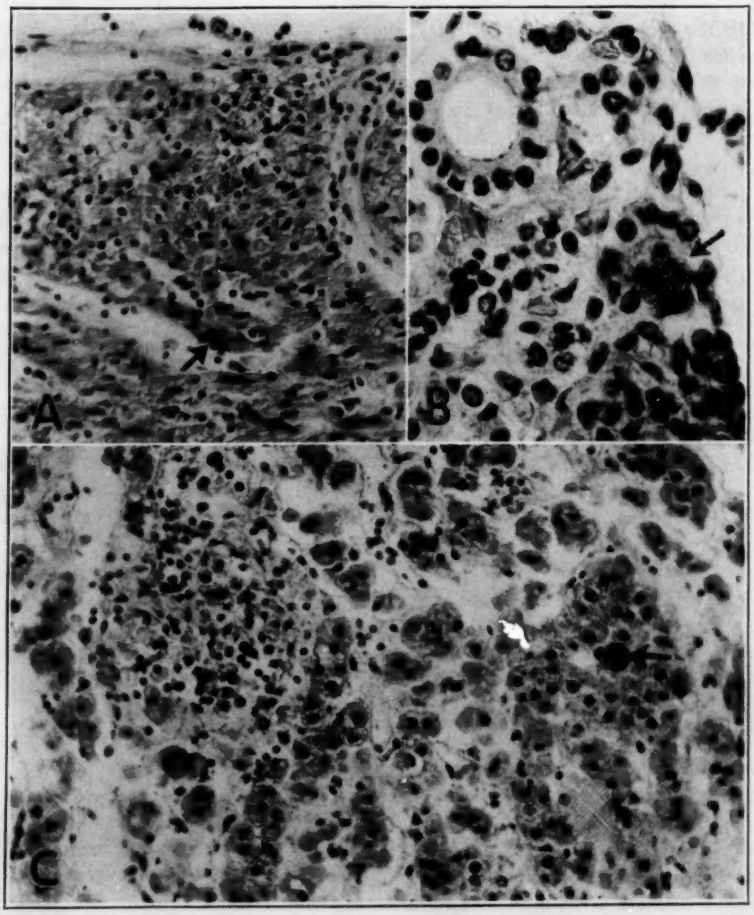

Fig. 10.—*A*. Diffuse myocarditis; infiltration by lymphocytes; parasitic cyst indicated by arrow; case 5; hematoxylin-eosin stain; × 230. *B*. Arrow indicates parasitic cyst within acinus; thyroid; case 5; hematoxylin-eosin stain; × 460. *C*. Focal inflammatory lesion in adrenal; arrow indicates parasitic cyst; case 5; hematoxylin-eosin stain.

3 by 1.5 mm. The circumscribed areas of discoloration in the basal ganglions and thalami were relatively infrequent and were intermediate in size between those occurring in the centrum ovale and those in the cortex, except for a single large lesion in the right thalamus, measuring 3 by 2 mm. The ventricles and the aque-

duct of Sylvius were normal in size, and their walls showed no gross abnormalities. The cerebellum, the brain stem and the spinal cord appeared normal on section.

The eyes were not examined.

Microscopic Observations at Autopsy.—In the lungs, hyperplastic, basophilic epithelial cells with large vesicular or hyperchromatic nuclei appeared in the ductuli and alveoli (fig. 8 *B*). Some of the alveoli were lined by a continuous layer of these large cells, in which mitotic figures or two or more nuclei were found occasionally. Not uncommonly the epithelial lining was incomplete, and isolated hyperplastic cells projected into the lumens of the alveoli or alveolar ducts. The cytoplasm of some epithelial cells was undergoing hyalinization, a number of cells seemed to have desquamated and many of the alveoli were filled with large mononuclear cells, hyalinizing cells and amorphous or fibrillar hyaline material, together with occasional polymorphonuclear leukocytes, erythrocytes and squamous epithelial cells aspirated from the amniotic fluid. Some of the alveolar walls were edematous and thickened by infiltrations of polymorphonuclear leukocytes, myeloid cells (including eosinophilic myelocytes) and nucleated red blood cells. Pyknosis and fragmentation of nuclei occurred in small areas. Toxoplasmas were numerous. Small groups of single parasites were discovered in the lumens of the ductuli and alveoli. In rare instances parasitized epithelial cells could be identified. More often large, closely packed aggregates of organisms, so-called cysts, were found in close proximity to the alveolar walls or free in the alveoli (fig. 9). At times a thin eosinophilic membrane surrounded these large clusters of parasites, and the appearance suggested heavily infected, greatly swollen epithelial cells (fig. 9). Smaller focal accumulations of toxoplasmas lay in the media of many arterioles (fig. 11 *A*). In a few places there was localized necrosis of the wall of an artery with fragmented nuclei and single parasites in the adventitia.

In the heart, there was widespread infiltration of the myocardium (fig. 10 *A*) and more localized infiltration of the endocardium by undifferentiated myeloid cells, eosinophils, nucleated red blood cells and lymphocytes. Focal necroses involving inflammatory cells and myocardial fibers were not infrequent. Numerous cardiac fibers contained toxoplasmas (fig. 10 *A*), as many as forty parasites being included in a single fiber.

In the adrenals, large and small focal necroses (fig. 10 *C*) occupied the permanent and fetal cortex. The surrounding capillaries were occluded by hyaline thrombi. At the margins of the necrotizing lesions were small numbers of large mononuclear cells, eosinophils and polymorphonuclear leukocytes. A parasitic cyst and a small group of single organisms were found in or near two of the localized lesions. Over parts of the ovaries the germinal epithelium was absent. In the cell cords the cells were swollen, hyaline or necrotic, with extensive fragmentation of nuclei. The neighboring stroma was edematous and contained small numbers of nucleated red blood cells, lymphocytes and myeloid cells. In the tunica albuginea lay a parasitic cyst, and a few single parasites were identified in the necrotic debris of the cell cords.

At the umbilicocutaneous junction was a thick mat of poorly preserved exudate in which no toxoplasmas were seen. The lumens and the intima of the umbilical blood vessels were free of lesions, but in the loose connective tissue surrounding the vessels and in the external layers of the media was a cellular infiltration of polymorphonuclear leukocytes and large mononuclear cells, with focal intensification at some sites. Occasional parasitic cysts were discovered deep in the loose tissue or in bundles of smooth muscle fibers. In a muscle of the anterior abdominal wall there was a small focus of necrotic fibers and reacting cells.

Large clusters of toxoplasmas without accompanying inflammation or necrotizing lesions were found in the acini of the thyroid (fig. 10 *B*), in the fibers of the abdominal, intercostal, and peritracheal muscles (fig. 11 *B*) and in subcutaneous adipose tissue. Neither parasites nor inflammatory or necrotizing lesions were apparent in the liver and spleen. In both of these organs extramedullary blood formation was active, and hemopoiesis was observed also in the pancreas and kidneys. A small inflammatory focus was present in the cortex of one kidney, and hyaline thrombi, into which fibroblasts and endothelial cells were penetrating, partially occluded the veins at the hilus. No parasites were found in the renal lesions. The esophagus showed superficial ulceration. The surface was covered

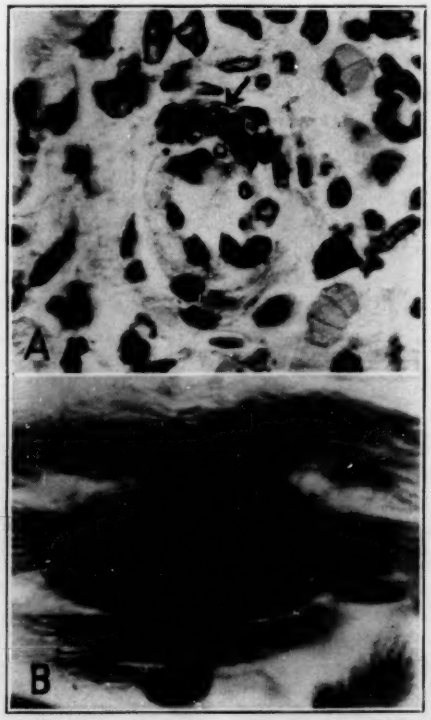

Fig. 11.—*A*. Arrow indicates parasitic cyst in wall of arteriole in lung; case 5; hematoxylin-eosin stain. *B*. Parasitic cyst in muscle fiber of striated muscle; no reaction about it; case 5; hematoxylin-eosin stain.

by many cells with fragmented nuclei, and in the submucosa were undifferentiated myeloid cells and deposits of fibrin. No toxoplasmas were discovered in these lesions.

Circumscribed lesions of two types were found in the cerebral cortex, the subcortical white matter, the centrum ovale, the basal ganglions, the diencephalon, the midbrain, the pons and the medulla and in all samples of the chief subdivisions of the spinal cord. The smaller and more frequent of these were sharply outlined, compact collections of closely approximated polygonal or irregular cells with dense eosinophilic cytoplasm and oval or irregular nuclei containing moderate amounts

of fine granular chromatin and having a well marked nuclear membrane. These granulomas (fig. 5 *C*) were definitely related to capillaries, and the epithelioid cells composing them appeared to be derived from the endothelial cells. Both cell types were frequently in mitosis. Central necrosis was rarely encountered in these lesions and was slight in degree where found.

The second type of lesion was larger, more diffuse, less distinctly outlined, less cellular, edematous and at times necrotizing and inflammatory (fig. 6 *A*). Its smaller representatives contained hypertrophied microglial cells, epithelioid cells of capillary origin and lymphocytes arranged irregularly and eccentrically about a congested capillary showing endothelial hyperplasia. At times these lesions showed central edema and necrosis of neural and neuroglial elements, with infiltration by small numbers of polymorphonuclear leukocytes and some lipid-laden phagocytes. The largest lesions showed extensive necrosis. Centrally cellular debris, lipid-laden phagocytes and some lymphocytes were present, while peripherally capillary congestion and endothelial hyperplasia, microglial hypertrophy and multiplication and infiltration by lymphocytes, large nononuclear cells and lipid-laden phagocytes were seen (fig. 8 *A*). In some instances, marginal granulomas were abundant. Even the largest of these necrotizing lesions was limited in extent; none reached the great size noted in the other cases.

Although both types of lesions were encountered in close proximity to the ventricular surfaces, no breakdown of the ventricular walls had occurred at any point. The leptomeninges showed occasional small focal collections of lymphocytes, large mononuclear cells and eosinophils, usually in relation to parenchymal lesions. No abnormal changes were noted in the choroid plexuses or ependyma.

Toxoplasmas were most numerous in the relatively infrequent larger necrotizing and inflammatory lesions. Here they were seen chiefly in the marginal inflammatory tissue, lying free, singly and in clusters or so-called cysts (fig. 12 *F*, *G* and *H*), and intracellularly in both forms within large mononuclear cells. Degenerating toxoplasmas were occasionally identified in the central necrotic zones. Micro-organisms were much less frequent in the smaller necrotizing lesions and were least often identified in the common miliary granuloma. A parasite undergoing binary fission was occasionally seen. In general, toxoplasmas were fewer in the central nervous system in this case than in previous instances of this disease. This seemed to be due to the fact that the infection was in an earlier phase.

Summary of Case.—A white girl, slightly premature, appeared normal at birth but gave evidence of a pulmonary infection on the second day of life. On the third day signs of circulatory failure supervened and fever was noted, and the child died when 3½ days old. Necropsy revealed the presence of toxoplasmas in the lungs, heart, brain, adrenals, ovaries, thyroid, striated muscles and adipose tissue. These had given rise to interstitial pneumonia, to acute diffuse myocarditis, to encephalomyelitis characterized by focal necrotizing and inflammatory lesions and miliary granulomas, and to focal lesions in the adrenals and ovaries. In the other organs in which they were present, the parasites had not produced any reaction. There were in addition acute omphalitis and acute esophagitis which did not appear to be due to Toxoplasma. There was extramedullary blood formation in the liver, the spleen, the pancreas and the kidneys.

DE LANGE'S CASE.[11]—Through the kindness of Prof. Cornelia de Lange, of Amsterdam, the Netherlands, it is possible to add another proved case to the annals of this disease. This case has been alluded to by us in a brief review of infantile toxoplasmic encephalomyelitis [11b] and is presented in detail here. In 1929, de Lange [11] reported this case as an instance of acquired internal hydrocephalus due to

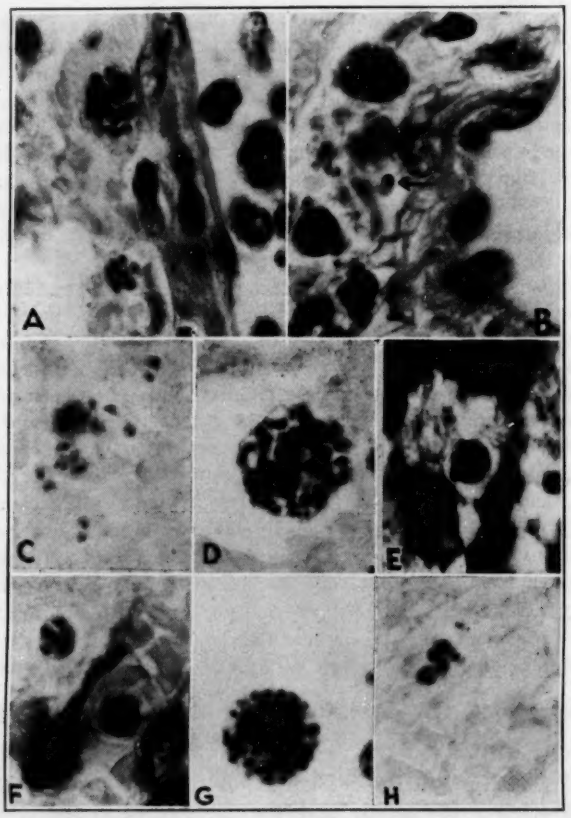

Fig. 12.—*A*. Two parasitic cysts adjacent to capillary in necrotizing lesion in wall of ventricle of cerebrum; case 3. *B*. Arrow indicates single parasite in cerebral lesion; case 3. *C*. Many single parasites and pairs of micro-organisms in necrotizing lesion in cerebrum; case 4. *D*. Parasitic cyst in cerebral lesion; case 4. *E*. Parasitic cyst in cerebral lesion; de Lange's infant. *F*. Cluster of parasites adjacent to a blood vessel in cerebral lesion; case 5. *G*. Parasitic cyst in cerebral lesion; case 5. *H*. Two clusters of parasites in cerebral lesion; case 5; hematoxylin-eosin stain.

partial occlusion of the aqueduct of Sylvius secondary to meningoencephalitis. A streptococcus was found in the ventricular fluid, but de Lange apparently did not believe that this was the cause of the

encephalitis. The gross and histologic features of the infection of the central nervous system in this child led the present authors to suspect that this might be a case of toxoplasmic encephalomyelitis. An opportunity to reexamine de Lange's slides revealed the presence of toxoplasmas in all the lesions.

Infant G (de Lange's report: Case 1 of acquired internal hydrocephalus), a white girl,[13] was normally delivered at term and weighed about 3,000 Gm. at birth. Because of feeding difficulty she lost weight, became dehydrated and was admitted to the hospital at 9 days of age. Her temperature was normal during the first two days of hospitalization, but thereafter it was continuously abnormal, varying considerably and ranging from a maximum of 106.9 F. to a minimum of 90.5 F., which suggested a disturbance of heat regulation. During the first few weeks of her stay in the hospital the infant had tremors of the arms. When she was 16 days of age, it was noted that the cranial sutures were wide and that the head was considerably enlarged, but the anterior fontanel was not tense. Although it was possible at first to nourish the patient, it grew progressively more difficult. She became increasingly drowsy, rarely moved and seemed to be barely alive. When she was 5 weeks of age, the fundi were reported to be normal. During the last week of life respiration became of the Cheyne-Stokes type, vomiting occurred frequently and the eyes remained constantly closed. The infant died four months after admission.

Gross Observations at Autopsy.—The greatest circumference of the head was 36.5 cm. The cerebrum showed flattening of the gyri, especially on the right and posteriorly. On coronal section just anterior to the chiasm, the left ventricle was found to be very widely dilated, so that the right ventricle was displaced toward the right. The corpus callosum was much narrowed, and the septum pellucidum was transparent. The corpus striatum was no longer recognizable and consisted bilaterally of yellowish white tissue. The entire thalamus was similarly degenerated (fig. 4). The aqueduct of Sylvius was not visible grossly, and the fourth ventricle was not enlarged. The midbrain and pons showed marked gross abnormalities (no further details given). Ventricular fluid obtained post mortem contained 1,400 mg. of protein per hundred cubic centimeters. Microscopically, it showed many mononuclear cells and many streptococci as well as diplococci and rod forms.

Microscopic Observations at Autopsy.—Sections of the degenerated corpus striatum, midbrain, medulla and cerebellum were examined. Cortical sections apparently were not taken.

The striatal architecture was no longer recognizable. The ventricular surface of the striatum was denuded of ependyma and lined by glial tissue which was sparsely cellular and contained some polymorphonuclears, macrophages, and many erythrocytes. External to this there was a layer of macrophages, mononuclear elements and calcium, and beyond that a band of mixed glial and connective tissue bounded by an extensive calcium deposit in which the vessels were thrombosed. Ganglion cells had disappeared completely. In addition to the deposit just described, calcium was found scattered through the rest of the degenerated striatum. No bacteria were seen aside from rare small clumps or rods (colon bacilli?).

A section of the midbrain revealed meningitis. The infiltration was mononuclear, and there was perivascular cuffing of penetrating parenchymal vessels.

13. The sex of the child, not noted in the original record, was learned in a personal communication from the author.

A wide band of periaqueductal parenchyma was markedly necrotic and contained thrombosed vessels, and in it the aqueduct could no longer be distinguished. The peripheral areas of the midbrain were better preserved, and in them perivascular infiltration and mononuclear cell clusters were found. The right substantia nigra and corpus quadrigeminum and the necrotic tissue dorsal to the aqueduct contained masses of calcium. More caudally the aqueduct was found to be occluded by a plug of tissue (presumably glial, considered by the author to have resulted from a hemorrhage). At the cephalic end of this mass the aqueduct was closed by a "neomembrane" (presumably fused ependymal granulations). The caudal portion of the aqueduct was not completely occluded, a narrow channel remaining. There was evidence of chronic ependymitis, both here and in the walls of the fourth ventricle. Hemorrhages were present in the periaqueductal region, in the pons and in the medulla, the majority being recent. There was no infiltration of the medulla, but there was exudate in the leptomeninges. The left pyramidal tract was smaller than the right.

The author described a series of ependyma-lined cavities in the brain stem and cerebellum related to the ventricular cavities. She considered these to be congenital abnormalities. In view of the chronic ependymitis, the question arises whether they might not have been secondarily buried ependymal pockets.

Some additional observations on the gross and microscopic observations made by us are appended. The photographs of the cross sections of the cerebrum revealed that the cerebral cortex and the centrum ovale were also involved. Both temporal lobes, particularly the left, showed parenchymal changes of the same type as those in the basal ganglions, and small lesions were also present in each centrum semiovale.

The microscopic changes were found to be similar to those in our own cases reported here. The intense parenchymal necrosis was associated in its more acute phase with infiltration by polymorphonuclear leukocytes and elsewhere with that of lymphocytes, plasma cells and large mononuclear cells, both diffuse and perivascular. The stains provided did not permit definite identification of eosinophils. Microglial activation with the formation of lipid-laden phagocytes, moderate astrocytosis and capillary proliferation with endothelial hyperplasia were present in the parenchymal lesions. There was an associated focal leptomeningitis in which the character of the cells was similar to that in the underlying neural tissue and which was marked by a moderate proliferation of leptomeningeal elements. At the margins of the larger lesions there were noted miliary granulomas (fig. 5*D*) composed of epithelioid cells of capillary origin resembling those described in our own cases. The granulomas showed no central necroses.

Parasites, both free and intracellular, were noted in many of the lesions (fig. 12*E*). They were oval or rounded bodies, the average size of which was 2 to 3 microns in length and 1.5 to 2 microns in width. They had acidophilic cytoplasm and eccentric, deeply staining, rounded chromatin bodies usually present at the blunter extremity. They occurred free, in clusters and within large mononuclear cells. These organisms had all the characteristics of Toxoplasma as seen in fixed tissue.

Summary of Case.—A white girl, delivered at term, was admitted to the hospital because of feeding difficulty at 9 days of age. She showed considerable fluctuations in temperature, which ranged from a high fever to subnormal levels, indicating a disturbance of heat regulation. Tremors of the arms were noted early, and evidence of hydrocephalus was seen when the infant was 16 days of age. Terminal vomiting was

frequent, Cheyne-Stokes respiration supervened and the child died at 4 months of age.

At autopsy, extensive necrotizing and inflammatory changes were found in the basal ganglions, in the thalamus and in the brain stem. Enlargement of the lateral ventricles was due in part to stenosis of the aqueduct of Sylvius, undoubtedly secondary to the inflammatory process, and in part to necrosis of their walls. Extensive calcification of the necrotizing lesions occurred. Miliary granulomas were frequent, and organisms morphologically identical with toxoplasmas were observed in the majority of the lesions. Although no sections of the spinal cord or of the eyes were available, it is clear that this case is similar in all essential respects to those previously described.

COMMENT

The 4 additional instances of infantile toxoplasmic encephalomyelitis reported here raise to 9 the authenticated cases recorded to date (table 1). The new clinical data furnished by the latest cases serve further to crystallize the clinical picture of this disease. It seems clear from a review of the symptoms and signs presented by these infants that a clinical diagnosis should be possible, and the following summary represents an attempt to establish diagnostic criteria.

Clinical Features.—A review of the clinical data in the 9 authenticated cases (table 1) indicates that it is a disease which affects young infants of either sex. Six of the infants were born at term and 2 were slightly premature; in the case of 1 the duration of gestation was not stated. Of the 4 infants whose condition at birth was recorded, respirations and color were good in 2, while 2 were moderately asphyxiated. One of the latter showed some delay in establishment of respiration. A fourth child was stillborn, since an internal hydrocephalus necessitated craniotomy to permit delivery.

The earliest symptoms and signs were observed within the first three days of life in 6 of the patients, while in 2 the onset may have been somewhat later, although certainly not later than the second and the sixth week of life respectively.

Onset.—In 2 cases the onset was with convulsions—generalized convulsions in 1 instance and right-sided jacksonian seizures rapidly becoming generalized in the other. A third infant, who survived birth by only two days, presented generalized muscular contractions at first and had convulsions shortly before death. A fourth patient had an enlarged head and right-sided facial paralysis at birth. The stillborn infant gave evidence of internal hydrocephalus in utero. In a sixth case, microphthalmos was noted at 3 days of age and blindness and enlargement of the head were observed at 3 months. A seventh infant

TABLE 1.—*Infantile Toxoplasmic Encephalomyelitis (Authenticated Cases to Date)*

Case	Location	Sex	Age at Death	Duration of Illness	Symptoms and Signs	Ocular Signs	Cerebrospinal Fluid	Roentgenographic Findings
Wolf and Cowen [1]..... (case 1) J. S.	New York	F	29 days	28 days	Convulsions (2d day), diarrhea, vomiting, labile body temperature, slight enlargement of head (24th day), disturbances in respiration	Yellowish white focal area of chorioretinitis, bilateral (27th day)	Xanthochromia, high protein content, pleocytosis (large mononuclears)	Skull: normal
Janku [1,4].....	Prague, Czechoslovakia	M	11 or 16 mo. (?)	8 or 11 mo. (?)	Marked hydrocephalus, blindness, convulsions, anorexia, vomiting	Yellowish white focal areas of chorioretinitis bordered by pigment in macular region, bilaterally; microphthalmos, unilateral (3d day)		
Torres [1,5].....	Rio de Janeiro, Brazil	F	2 days	2 days	Convulsions (2d day)			
Richter [2,7b].....	Chicago	F	7 wk.	1 wk. (?)	Convulsions (terminal), opisthotonos, fever, "cold"	.....	Xanthochromia, high protein content, pleocytosis (mild)	
Wolf, Cowen and Paige [3a,b] (case 2) C. D.	New York	M	31 days	28 days	Convulsions (3d day), vomiting, sensory and motor signs of cervical involvement with subarachnoid block, labile body temperature, disturbances in respiration	Reddish brown areas of chorioretinitis in macular regions, bilaterally; enophthalmos, unilateral (3d day)	Xanthochromia, high protein content	
Paige, Cowen and Wolf (case 3) L. M.	New York	F	9 wk.	9 wk.	Hydrocephalus (at birth), twitching of lower extremities, labile temperature (usually subnormal), convulsions (terminal)	Membranous masses in each vitreous; microphthalmos and enophthalmos, bilateral (12th day)	Xanthochromia, increased protein	Skull: calcification in brain (6th day), hydrocephalus
Paige, Cowen and Wolf (case 4) B. R.	New York	M Negro	Craniotomy, stillborn		Fetal hydrocephalus	Microphthalmos and enophthalmos, unilateral	.....	Maternal: fetal hydrocephalus
Paige, Cowen and Wolf (case 5) A. M. T.	New York	F	3½ days	1½ days	Respiratory difficulty (2d day), edema, cyanosis, terminal mild fever	No examination	No examination	No examination
deLange [11].....	Amsterdam, Netherlands	F	4 mo.	3½-4 mo.	Hydrocephalus (16th day), fever (labile temperature, often subnormal), vomiting, tremors of arms	Fundi normal (5th week)		

was admitted to the hospital when 9 days old because of feeding difficulty, had fever on the twelfth day and on the sixteenth day was found to have enlargement of the head. An eighth patient had fever in the sixth week of life and convulsions during the last twenty-four hours. In the ninth case respiratory difficulty occurred on the second day.

Symptoms and Signs.—Convulsive Seizures: All but 2 of the viable infants suffered convulsions at some time during their illness. As already noted, 3 of the infants had convulsive seizures soon after birth, and of these 1 died shortly after the onset of the attacks on the second day of life. Another of the 3 had six or seven generalized convulsions on the second day, without recurrence until the fourth week. In the third, convulsions began on the third day and recurred at intervals of several days, ceasing by the end of the second week. Of the remaining 5 infants, 1 was stillborn, 1 had generalized convulsions for a short period during his rather protracted illness, 2 had convulsions in the terminal stages of their illness and the last had no seizures.

Internal Hydrocephalus: There was internal hydrocephalus in 6 patients. In one this was noted in utero and was suspected as early as the end of the seventh month of gestation. In 3 others the internal hydrocephalus was also the outstanding manifestation of the disease, was observed immediately after birth or early in the course (sixteenth day; third month of life), and was progressive. In a fifth patient, slight enlargement of the head was found on the twenty-fourth day, and dilatation of the lateral ventricles was confirmed by ventricular puncture. In the sixth case, mild hydrocephalus was found at autopsy.

Ocular Signs: In 3 patients microphthalmos was noted, unilateral in 2 and bilateral in the other patient. In 2 of the 3 and also in a fourth patient, enophthalmos was present. Five of the infants had striking chorioretinal lesions; in the cases of the other 4, such lesions were not excluded by pathologic examination. The process was bilateral. In 3 of the cases the lesions as seen by ophthalmoscope were circular or oval, yellowish white or reddish brown, sharply marginated, slightly elevated or concave patches, sometimes bordered and studded by dark pigment and varying in size from a little less than 1 to 5 disk diameters. They were usually situated in the macular region. They were variously interpreted as focal inflammation, glioma or the result of hemorrhage. The histologic appearance of the chorioretinal lesions in the stillborn infant was identical with that in the 3 preceding cases and should have been similar ophthalmoscopically. In the fifth subject, membranous masses posterior to the lens were seen in each eye. These were thought to be persistent tunica vasculosa lentis, retinoblastoma or detachment of the retina. Histologically, they proved to be partially organized granulation tissue which had grown into the vitreous from extensive patches of chorioretinitis. In this instance the lesions were first observed

ophthalmoscopically between the twelfth and the seventeenth day of life; in 2 cases they were seen during the fourth and the fifth week of life respectively, while in another they were first observed some time during the latter half of the first year of life. It is possible that if ophthalmoscopic examination had been made sooner ocular lesions might have been revealed earlier in the course of the disease. In the stillborn infant, it is obvious that the chorioretinal lesions must have had their inception during intrauterine life.

Neurologic Signs and Symptoms: The neurologic signs were variable, since the lesions were disseminated throughout the brain and spinal cord. Generalized convulsions were frequent, as previously noted; tremors or twitchings of the extremities were common, and retraction of the head or opisthotonos occasionally occurred. Vomiting was not uncommon. Nystagmus or nystagmoid movements of the eyes, deviation of the head and eyes to one side, impairment of ocular movements, blindness, papilledema and abnormal pupillary reactions were sometimes noted. The deep and superficial reflexes showed no constant changes. There was spastic contraction of the limbs in 2 instances. One patient showed evidence of high cervical transverse myelitis and subarachnoid block, with which a Horner's syndrome was associated.

Temperature: In 2 of our cases in which a complete temperature record is available from birth, the temperature was normal during the early weeks of the illness. In these cases and in a third, observed only during the last few days of the patient's life, the temperature was markedly labile terminally, varying from high fever to subnormal levels. Wide swings of temperature often occurred on the same day. In a fourth case the patient showed a similar lability of temperature during the major portion of the illness, beginning in the second week of life and continuing until death, at 4 months of age. In these 4 cases there was evidently a disturbance in heat regulation, coming on terminally in 3, which may have been due to the lesions in the floor of the third ventricle. A fifth patient, who lived for only three and one-half days, showed a normal temperature on the first two days, with a rise to 101 F. on the third day and a return to normal on the day of death. In 3 cases the temperature record is incomplete. In 1 instance it was given as normal on the patient's admission to the hospital and subnormal at death; in another there was no reference to the temperature, and in a third it was stated that there was fever five days before the patient's admission and that the temperature on admission was 101.6 F. In general it may be said that there is a tendency toward a normal temperature early in the disease, and toward an unstable temperature in the later stages, with frequent drops to subnormal.

Laboratory Findings.—Blood: Examination of the blood was reported in 5 cases. In 3 there was a relative leukopenia, the leukocyte

count varying from 5,200 to 8,000 per cubic millimeter. These counts were made during the first month of life, when the average normal count is approximately 12,000 cells per cubic millimeter. In 1 of these cases and in a fourth case there was a leukocytosis terminally, but in each of these a complicating bacterial infection was present at that time. In a fifth instance the blood count was normal during the three and one-half day span of the patient's life. There were no consistent changes in the differential count. A questionable eosinophilia was noted in 1 instance. In 2 cases there was anemia of moderate degree.

Cerebrospinal Fluid: The cerebrospinal fluid was examined in 4 cases. The fluid obtained by lumbar or cisternal puncture was under normal pressure. It was xanthochromic, showed a high protein content (Pandy reaction 4 plus; prompt clotting in 1 case), and in 2 instances exhibited pleocytosis. The cell studies were unsatisfactory, but in 1 instance lymphocytes predominated in the smears. The spinal fluid dextrose and chloride contents were 32 mg. and 674 mg. per hundred cubic centimeters respectively in 1 instance and 43 mg. and 616 mg. per hundred cubic centimeters in another.

Ventricular fluid was examined in 2 cases. A number of examinations were made, and in each case the cerebrospinal fluid pressure was somewhat increased when first measured and normal on subsequent punctures. The fluid was xanthochromic and usually hazy or turbid. In 1 case there was a distinct pleocytosis, with over 1,000 cells per cubic millimeter; mononuclear elements predominated; occasional eosinophils were found in one smear. A high protein content (Pandy reaction 2 plus to 4 plus) was the rule. The dextrose and the chloride content respectively were 8 mg. and 515 mg. per hundred cubic centimeters in 1 case and 23 mg. and 653 mg. per hundred cubic centimeters in the other.

In the spinal and ventricular fluids of 3 patients red blood cells, ranging from 180 to "many" per cubic millimeter, were found.

Roentgenographic Examination.—A roentgenogram of the skull in 1 case, in addition to revealing signs of internal hydrocephalus, showed the presence of small calcium deposits in the cerebrum at the age of 6 days, which were interpreted as being located in the frontal and occipital lobes. At autopsy, these were found to be calcified lesions. In 3 other cases a considerable amount of calcium was found in the lesions at postmortem examination, and it seems likely that had the calcification been sought for roentgenographically in these cases it might well have been demonstrated during life. In 1 instance a pelvic film of the mother revealed evidence of internal hydrocephalus in the fetus in utero; in that case calcification of cerebral lesions, as seen histologically, was sufficiently advanced to have been detectable roentgenographically had the infant survived delivery.

Possible Additional Instances of Infantile Toxoplasmic Encephalomyelitis.—Hassin (1927)[14] reported an instance of diffuse infection of the central nervous system in a 15 day old infant who had multiple congenital malformations. In reviewing this case in 1940,[15] the author compared it to the reported cases of toxoplasmic encephalomyelitis and stated that he believed it to be an example of the disease. "Minute bodies" (Da Fano) present in the lesions were thought in retrospect to be imperfectly stained toxoplasmas. Unfortunately the gross and microscopic specimens were no longer available for reexamination. An analysis of the original description and a study of the illustrations render it difficult to accept this case as an instance of toxoplasmic encephalomyelitis. The distribution and morphology of the lesions and the predominantly polymorphonuclear reaction do not resemble the findings in the known cases of infantile toxoplasmic encephalomyelitis. The "minute bodies," with their indefinite and variable structure, cannot be accepted as proved toxoplasmas.

Pinkerton and Weinman (1940)[8] reexamined a case previously described by Hertig[16] of a premature infant dying twenty-four days after birth with multiple abscesses in the brain, peritonitis, omphalitis and terminal bronchopneumonia. A number of bacteria were cultivated from the brain and peritoneal fluid. Protozoa, thought by Hertig to be Sarcocystis, were later considered by Pinkerton and Weinman to be toxoplasma. These were found in the brain, the spinal cord, the lungs, the adrenals and the heart. Little or no inflammatory reaction or necrosis was present about them. The absence of pathologic lesions due to toxoplasmas distinguishes this case from those of infantile toxoplasmic encephalomyelitis and classes it as an instance of infantile infestation by this protozoon without reaction. Its relationship to the cases described here will be discussed in the next section.

Visceral Lesions.—A complete autopsy was performed in 7 of the 9 proved instances of infantile toxoplasmic encephalomyelitis, and in 3 cases involvement of tissues other than the central nervous system was noted (table 2). In 2 of these, extraneural lesions were minor, while in 1 they predominated. This patient (case 5) suffered from an extensive interstitial pneumonia which was essentially like that described in adult toxoplasmosis, points of resemblance being the hypertrophy and parasitization by toxoplasmas of the alveolar epithelial cells and the interstitial inflammation. All 3 of the infants having extraneural

14. Hassin, G. B.: Acute (Epidemic?) Encephalitis: Report of a Case in a New-Born Twin, with Histologic Observations, Arch. Neurol. & Psychiat. **18**: 44-55 (July) 1927.

15. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, ed. 2, New York, Paul B. Hoeber, Inc., 1940.

16. Hertig, A. T.: Sarcosporidia in the Myocardium of a Premature Infant: Report of a Case, Am. J. Path. **10**:413, 1934.

lesions (case 4, case 5 and Torres [5]) had acute diffuse myocarditis; this was true as well of the reported instances of adult toxoplasmosis.[17] Parasitized myocardial fibers without necrosis or inflammation were also observed.

Small necrotizing and inflammatory foci were found in the adrenals in 2 instances (cases 4 and 5), and similar adrenal lesions were reported in 1 instance of adult toxoplasmosis.[8] The striated muscles in 2 infants (case 4 and Torres [5]) showed focal inflammatory lesions and parasitized muscle fibers without reaction, while in 1 (case 5) they showed only

TABLE 2.—*Visceral Lesions in Cases of Infantile Toxoplasmic Encephalomyelitis (Infantile Toxoplasmosis)*

	B. R. Case 4	A. M. T. Case 5	Torres [5]	Pinkerton and Weinman [8]
Central nervous system	+	+	+	T
Choroid and retina	+	..	..	..
Heart	+ and T	+	+	T
Lungs	—	+	..	T
Spleen	—	—	—	..
Liver	—	—	—	..
Pancreas	—	—	..	..
Adrenal	+ and T	+	..	T
Kidney	—	—	—	..
Testes or ovaries	—	Ovaries +	..	..
Uterus	..	—	..	..
Bladder	..	..	..	..
Gastrointestinal tract	..	..	..	..
Thyroid	..	T	..	..
Thymus	—	..	—	..
Pituitary	..	..	..	..
Striated muscles	+ and T	T	+	..
Skin and subcutaneous tissue	—	T	T	..
Bone marrow	—	—	..	..
Umbilicus	—	T	..	..

+ = Lesions due to toxoplasmas.
— = Examined; no lesions due to toxoplasmas found.
T = Toxoplasmas without lesions.

scattered parasitized fibers. In this last case there were also focal inflammatory lesions in the ovaries, and there were toxoplasmas without reaction in the thyroid and adipose tissue. In none of the cases of infants with extraneural lesions has there as yet been reported involvement of the liver, spleen or lymph nodes, although focal necrotizing and inflammatory lesions have been described as present in these organs in adults with toxoplasmosis.[17] Toxoplasmas without the formation of lesions were found in the subcutaneous tissue in 1 infant (Torres [5]). Focal inflammatory lesions with or without toxoplasmas were described in the corium and the subcutaneous tissue in 3 adults (Pinkerton and Weinman,[8] Pinkerton and Henderson [9]). Reference has been made in

17. Pinkerton and Weinman.[8] Pinkerton and Henderson.[9]

a previous section to an infant reported [8] as having toxoplasmic infestation of the lungs, adrenals and heart, as well as of the brain and spinal cord, without the production of any specific lesions. The distribution of parasites in this case was similar to that in the instances of infantile toxoplasmic encephalomyelitis with extraneural lesions, linking it to them.

In all the instances of human toxoplasmosis thus far recorded there has been involvement of the central nervous system, with or without lesions in the other organs. In the 3 adults,[17] the neural lesions were few and small, while the visceral lesions, among which pneumonia was prominent, were extensive. In the single juvenile patient coming to autopsy [10] lesions in the central nervous system were as few as those in the adults; the other organs were not examined. In 1 infant (case 5), as in the adults, visceral lesions, especially in the lungs, predominated. While the lesions in the central nervous system were milder than those in the other infants, they seemed more severe than those in the juvenile and in the adult patients.

This difference in the distribution of lesions with age is interesting in that it parallels that observed with experimental toxoplasmosis in mice.[3c] The infant mice with toxoplasmosis exhibited a very severe encephalomyelitis with relatively few visceral lesions, while the adults showed widespread lesions in extraneural tissues with a varying degree of involvement of the central nervous system.

It would seem proper to group together those instances of toxoplasmosis in which symptoms and signs begin in infancy. These would include (*a*) the cases of infantile toxoplasmic encephalomyelitis, (*b*) cases of toxoplasmosis with visceral lesions predominating, and (*c*) cases of generalized toxoplasmic infection without definite lesions. All three categories should be classed under the general heading of cases of infantile toxoplasmosis.

Prenatal Inception of the Disease.—Pathologic studies and reviews of the clinical history in cases of this disease, both before [18] and after it was proved [3a,c] to be a form of toxoplasmosis, led to the conclusion that the infection was congenital. In 2 cases (Wolf and Cowen, case 1,[1] and Torres [5]) convulsions occurred on the second day of life, and 1 of the patients died on that day. In a third case (Wolf, Cowen and Paige, case 2 [3b]) the patient had generalized convulsions on the third postnatal day. In a fourth instance (Jankû [4]) microphthalmos was noted on the third day after birth. The onset of symptoms and signs so soon after birth was noteworthy. Strong corroborative evidence was provided by the pathologic changes noted in some of these cases. The chronic appearance of the pathologic lesions, which were often exten-

18. Wolf and Cowen (footnotes 1 and 2). Jankû.[4] Torres.[5] Richter.[7b]

sively calcified, made it seem unlikely that they could have developed during the short extrauterine period. These findings suggested that the disease had begun as a fetal encephalomyelitis.

The considerations which weighed against this assumption were (1) that the mothers were all apparently healthy and some bore healthy children prior and subsequent to the birth of the infected child; (2) evidence of placental infection was lacking, and (3) evidence of the occurrence of adult human toxoplasmosis had not been furnished. The last objection is now overcome, with the recent demonstration of toxoplasmosis in adults. The first inconsistency, the fact that the mothers seemed healthy, may mean, as has been suggested elsewhere, that they harbored a latent infection. The common occurrence of clinically inapparent toxoplasmic infection in animals would lend support to such a possibility. Placentas have not, as yet, been available in these human cases, except in 1 instance, in which the poor state of preservation made it unsatisfactory for study.

The cases of this disease described in the present paper prove that infantile toxoplasmosis may begin as a fetal encephalomyelitis, as has been stated in a preliminary report.[19] One infant (case 4) had given evidence of hydrocephalus in utero, so that craniotomy was necessary for delivery. On pathologic examination the stillborn fetus presented an advanced toxoplasmic encephalomyelitis with extensive calcification of the lesions and associated chorioretinitis. Toxoplasmas were abundant in the lesions. In this instance there can be no doubt that the infection was acquired during intrauterine life. A second infant (case 3) gave evidence of internal hydrocephalus within a few hours of birth. The enlargement of the head progressed rapidly thereafter. At autopsy the enlargement of the ventricles was found to be secondary to occlusion of the interventricular foramens. The latter was obviously the result of a toxoplasmic encephalomyelitis, verified not alone by the typical pathologic picture and the presence of the protozoa in the lesions, but also by the transmission of the infection to animals. Intracerebral calcification, identified roentgenographically on the sixth day of life in this case and noted in toxoplasmic lesions post mortem, gave evidence of a chronic infectious process which could hardly have developed within such a short period after birth. These facts point to the prenatal inception of the disease in this child. The third infant (case 5) became ill on the second day of life and died at the age of 3½ days. This neonatal onset of symptoms would suggest that in this instance, too, the infection began in utero.

Detailed inquiries into the past histories of the mothers of these infants have revealed no evidence of any illness which might have been

19. Wolf, A.; Cowen, D., and Paige, B. H.: Fetal Encephalomyelitis: Prenatal Inception of Infantile Toxoplasmosis, Science **93**:548-549, 1941.

a toxoplasmosis. Contacts with potential Toxoplasma-bearing animals have been referred to in previous reports. The mother of the patient in case 3 had had no significant contact with potential carriers. In case 4 there had been a mild infestation of the home by mice. In none of these instances is there any direct evidence that the rodents or birds mentioned had a toxoplasma infection or that the mothers acquired such an infection. The question of a possible insect vector has been raised, and the intermediation of such a secondary host has been considered as probable; but no definite proof has as yet been furnished on this point. Aside from tick bites suffered by the father without known sequelae, the parents had no significant contacts with animals in case 5.

In an attempt to ascertain the existence of maternal infection, tests for neutralizing antibodies in the blood of the mothers have been undertaken. The technic for demonstrating antitoxoplasmic activity of the serum is based on a method described by Sabin and Olitsky.[20] The mothers of 2 infants described in this report (cases 3 and 4) with proved toxoplasmosis have been studied. Their serums, normal control serums and physiologic solution of sodium chloride were mixed with varying dilutions of suspensions of mouse brain infected with Toxoplasma and inoculated intradermally into rabbits. The development of cutaneous lesions typical of those caused by Toxoplasma was used as an indicator. There was definite inhibition of the formation of such lesions by the serums of the mothers of the infected children. This demonstration of maternal neutralizing antibodies yields some evidence that the mothers were infected or that they still harbored a latent infection.

Further Comment on Pathogenesis: In a discussion of the pathogenesis of the disease in a previous paper,[1] it was suggested that if transmission of the infection occurred during intrauterine life it might be assumed that the parasite entered the fetal circulation by way of the placenta. The placenta was examined in only 1 of the 9 cases of infantile toxoplasmosis (case 4), and no evidence of placental infection was obtained. No direct proof of this hypothesis has as yet been forthcoming. Later we[3b] considered the possibility of vaginal infection of the mother, with extension of the infection to the uterine contents, though this seemed unlikely. Case 5 would seem to offer some evidence that this may possibly be true. The severity of the pulmonary lesions, the large numbers of toxoplasmas and the presence of such parasites in abundance in the alveolar spaces would suggest the aspiration of infected amniotic fluid. The presence of toxoplasmas in the walls of pulmonary vessels and the type and distribution of lesions in other

20. Sabin, A., and Olitsky, P. K.: Toxoplasma and Obligate Intracellular Parasitism, Science **85**:336-338, 1937.

organs resembling that seen in experimental toxoplasmosis [3c] following intravenous inoculation suggest that the infection may possibly have been primary in the lungs and have been conveyed to other organs by way of the blood stream. The premature rupture of the membranes in 3 cases (case 2,[3b] case 3 and case 4) from several days to three or four weeks before delivery indicates the fashion in which such an infection of the amniotic fluid might occur. It must be pointed out, however, that in the single case in which severe pulmonary infection occurred (case 5), the membranes were intact till shortly before delivery. That microorganisms might conceivably pass through intact membranes or through slight premature ruptures to infect the amniotic contents has been postulated in some instances of congenital pneumonia in newly born infants (Johnson and Meyer [21]). The question of the occurrence of spontaneous vaginal toxoplasmosis in human beings has not as yet been answered, although experimental infection of mice has been produced by this route.[22]

The view has been previously expressed that parasites enter the neural parenchyma by way of the blood vessel walls, where they are met by a protective reaction in the latter, expressed by the production of the granulomas. That these are the first response to the infection is rendered likely by the findings in case 5, in which they were present almost to the exclusion of other lesions and in which the involvement of the central nervous system seemed comparatively early. When such a defense reaction does not occur or perhaps is overwhelmed, intense diffuse inflammation of the parenchyma with necrosis supervenes.

DIAGNOSIS

In a previous report,[3b] criteria for the establishment of the clinical diagnosis of infantile toxoplasmic encephalomyelitis were outlined. The additional material in the preceding sections on clinical features of the disease confirms these suggestions. Briefly, the diagnosis should be rendered possible by the following data:

1. A history of onset of symptoms at birth or during early infancy.

2. Varied neurologic symptoms, including convulsions and hydrocephalus (although these may be absent, as in case 5).

3. Ophthalmoscopic observation of chorioretinitis, frequently in the macular region; yellowish white or reddish brown, round or oval, slightly depressed or elevated patches with irregular spotty black, often marginal, pigmentation.

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21. Johnson, W. C., and Meyer, J. R.: A Study of Pneumonia in the Stillborn and Newborn, Am. J. Obst. & Gynec. **9**:3-19, 1925.

22. Mesnil, F., and Sarrailhé, A.: Toxoplasmose expérimentale de la souris: Passage par les muqueuses, conservation du virus dans le cadaver, Compt. rend. Soc. de biol. **74**:1325-1327, 1913.

4. Roentgenographic demonstration of intracerebral calcification.

5. Determination of clinically inapparent internal hydrocephalus by pneumoencephalography.

6. Xanthochromia, round cell pleocytosis and high protein content of the cerebrospinal fluid (lumbar or ventricular).

7. The recovery of toxoplasmas from the blood or cerebrospinal fluid by inoculation of mice, rabbits or both intracerebrally and intraperitoneally.

8. Demonstration of Toxoplasma-neutralizing antibodies in the blood of the infant or of the mother.

SUMMARY

Three additional cases of infantile toxoplasmic encephalomyelitis are presented. The condition was identified by the typical pathologic lesions containing toxoplasmas and in 1 instance by the transmission of the infection to rodents. In 1 case, in addition to the encephalomyelitis, there were extensive visceral lesions, notably in the lungs, heart and adrenals. In another instance visceral lesions were less marked.

A fourth case, previously reported in the literature as an instance of acquired internal hydrocephalus, is identified as a case of toxoplasmic encephalitis by reexamination of the microscopic specimens and the finding of characteristic lesions and micro-organisms.

The observations in our own cases make it certain that at least some and perhaps all of the instances of infantile toxoplasmic encephalomyelitis begin as a prenatal toxoplasmosis.

A summary of the clinical findings in the cases in which autopsy has been performed to date permits the outlining of diagnostic criteria for the disease which should lead to its identification during life.

Dr. B. P. Watson permitted us to use the records of cases 4 and 5, and Dr. W. E. Caldwell supplied the record of case 3. Dr. Cornelia de Lange sent us slides and photographs of the lesions in her case and gave us permission to report further on it.

Case Reports

ECTOPIA CORDIS

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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AND
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MUSKOGEE, OKLA.

A case of ectopia cordis abdominalis occurred in our service at St. Vincent's Infant and Maternity Hospital recently.

REPORT OF CASE

History and Course.—The mother, S. F., a primipara aged 23 years, entered the hospital Sept. 15, 1941, in active labor. She came under observation for prenatal care May 23, 1941, and the course of the pregnancy was normal. Her blood pressure and urine were normal on repeated examination, and her Kahn reaction was negative. Her pelvic measurements were adequate and the estimated date of delivery was October 24. At the onset of labor, a diagnosis of placenta praevia marginalis was made, and Drs. J. X. Bremner and A. C. Wise after manual cervical dilation made a midforceps delivery.

In the mother's family history there was no known instance of congenital defect. The father had a niece with a congenital cardiac lesion.

At birth, P. F., a girl weighed 5 pounds 12½ ounces (2,522 Gm.) The first recorded axillary temperature was 97.6 F. There was considerable mucus, which had to be aspirated with a tracheal catheter before the infant could breathe. The cry was weak. There were no abnormalities except those associated with the heart and the anterior abdominal wall. A ventral hernia (fig. 1), approximately 6 by 6 cm., extended from the xiphoid process to a point caudad to and including the umbilicus. Its lateral borders were the rectus abdominis muscles. The sternum was normally fused. The skin overlying the hernia was darker than the surrounding skin, was thin and stretched and contained small distended blood vessels. The lower border of the darkened skin included the umbilicus. Immediately adjacent to the umbilical cord the skin was ecchymotic. The hernial sac included in its upper portion, a visible and palpable pulsating firm mass identified as a ventricle, probably the left. Loops of compressible bowel were visible and palpable through the thin hernial wall in the lower portion. Heart sounds were heard loudest over the pulsating mass but could also be heard in the usual precordial area. No murmur was detected at this time.

The infant was placed in a heated crib, and the pulsating hernial mass was covered only lightly with sterile gauze. On September 26, the eleventh day of life, the cord came off and at its site a flat 5 cm. crust was left which in ten days healed, leaving a smooth scar.

From St. Vincent's Infant and Maternity Hospital.

On October 11, when the child was almost 4 weeks of age, a murmur appeared loudest in the second interspace to the left of the sternum. The murmur was audible over the entire chest and over the pulsating mass in the abdomen. The portion of the heart present in the hernial sac extended well above the plane of the abdominal wall. Systole and diastole were clearly visible, and the organ could be held between the fingers with no apparent embarrassment to the child. The pulsations were strong and regular and gave one the sense of a very firm and excellent muscle tone. No further changes occurred in the cardiac condition until shortly before death.

Fig. 1.—The ventral hernia contains loops of intestine and both ventricles of the heart.

In accordance with our usual procedure in the care of the newly born, the infant was given nothing by mouth during the first twelve hours. Eight cubic centimeters of raw human milk was fed from a nursing bottle every four hours after the initial twelve hour starvation period. The amount was increased each day, and on the fourth day of life it was complemented with a pasteurized milk of low curd tension. At the end of the first week, the infant weighed 4 pounds 15 ounces (2,240 Gm.), a loss of 9 ounces (255 Gm.) from its birth weight. By the end of the second week, it had regained 7 ounces (198 Gm.). On October 7, when the child was 3 weeks old, percomorph liver oil and orange juice were added to the diet. On the same day, 12 cc. of whole blood was given intramuscularly. The infant took its feedings poorly. From October 9 to 19, 5 per cent

dextrose in physiologic solution of sodium chloride was given subcutaneously in amounts of approximately 50 cc. daily. On October 15, the infant had a nasal discharge, some small pustular cutaneous lesions and fever. Sulfadiazine (2-[para-aminobenzenesulfonamido]-pyridine), 2 grains (0.12 Gm.), was given four times daily from October 15 to 22. The dose was then reduced to 2 grains three times daily until the treatment was discontinued, on October 26. The infant tolerated the drug well; the nasal discharge and the eruption disappeared, and the temperature dropped to normal. On October 16, a small dose of vitamin B complex was introduced into the diet. The gain in weight was irregular; at the age of 1 month the infant weighed 5 pounds 6 ounces (2,438 Gm.), at the age of 2 months she weighed 6 pounds 10 ounces (3,005 Gm.) and on November 26, two days before death, she weighed 6 pounds 15½ ounces (3,161 Gm.).

Laboratory Examinations.—Blood Counts: Counts were made on Oct. 8 and Oct. 20, 1941. On the first date the hemoglobin content was 93 per cent; there

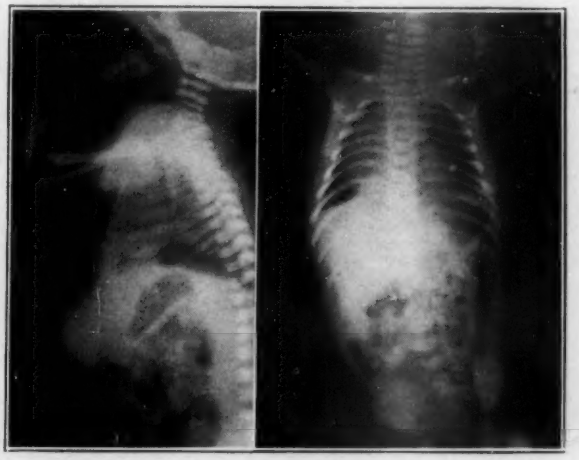

Fig. 2.—Roentgenograms taken on the third day of life.

were 4,500,000 red cells and 10,800 white cells, with 76 per cent lymphocytes, 5 per cent monocytes, 4 per cent eosinophils, 3 per cent myelocytes, 8 per cent stab forms, 2 per cent segmented forms and 2 per cent normoblasts. Anisocytosis and large platelets were noted. On October 20, the hemoglobin content was 103 per cent; the red cells numbered 5,050,000 and the white cells 23,100; the differential count showed 47 per cent lymphocytes, 6 per cent monocytes, 9 per cent eosinophils, 2 per cent premyelocytes, 7 per cent myelocytes, 1 per cent stab forms and 22 to 23 per cent segmented forms; normoblasts were seen. The mean corpuscular volume was 51 per cent; the mean corpuscular hemoglobin concentration, 31 per cent, and the mean corpuscular diameter, 8 microns.

Urinalysis: On two occasions, October 7 and October 20, examination of the urine showed nothing abnormal except for a slight trace of albumin.

Roentgen Examinations.—The report of Dr. John H. Gilmore on the fluoroscopic examination and roentgenogram of September 18 (fig. 2) was as follows:

"There is a large unusual prominence in the upper abdominal region, assuming an oval configuration and projecting well beyond the usual anterior abdominal

limitation shadow—a congenital ventral hernia. This hernia contains bowel shadows designated by the presence of gas. Fluoroscopically observed, this hernia is most prominent to the right of the midline below the costal margin, corresponding to the visible pulsation externally.

"The sternum visualized laterally presents an unusual wide separation between the region of the xiphoid process and the anterior ends of the ribs. The diaphragmatic domes can be identified up to their usual anterior attachments, and there is a wide space between this point and the lower center of ossification of the sternum. The pulmonary fields appear clear. The usual intrathoracic cardiac space is occupied by a very thin shadow, which is by far more prominent on the right than on the left. This shadow is only faintly visible fluoroscopically and does not pulsate. The air passages visualized are somewhat more anteriorly spaced than normal.

"Opinion: The pathologic picture described may be accounted for by the following abnormality: a congenital ventral hernia which involves the anterior

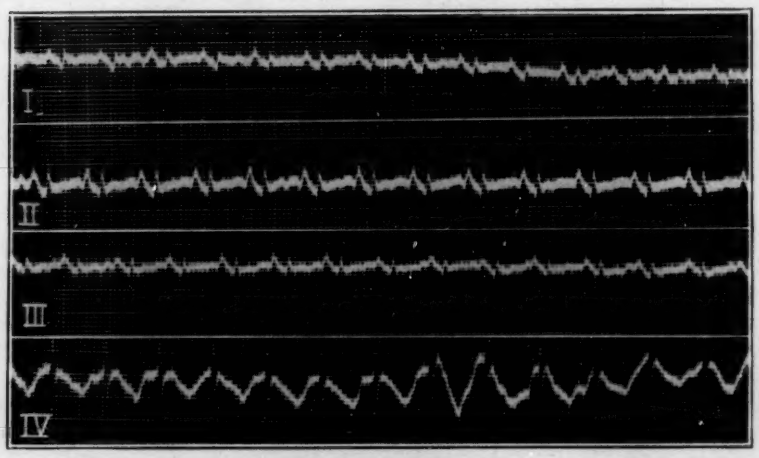

Fig. 3.—Electrocardiogram taken on the second day of life.

wall of the chest and the upper part of the abdomen at the anterior attachment of the diaphragm, which contains small bowel, a portion of the duodenum, pylorus, a portion of the liver and a majority of the cardiac structure. The left ventricle is apparently in a position to the right of the midline as a result of complete rotation in its descent into the hernial sac. The shadow present in the usual cardiac position in the thorax is accounted for partially on the basis of thymus shadow and remaining pericardial attachments."

A second roentgenogram, taken November 4, when the infant was 7 weeks of age, was reported on by Dr. Gilmore as follows:

"Reexamination of this baby's abdomen and chest in anteroposterior and lateral positions reveals conditions as described on the previous study except that the hernial sac is larger and contains more bowel shadow at this time."

Electrocardiograms.—First Examination.—An electrocardiogram taken on September 17 (fig. 3), when the infant was 2 days of age, was reported on by Dr. Lawrence E. Hines as follows: rate, 130; PR interval, 0.16 second; QRS interval,

0.06 second; rhythm, sinus mechanism; P waves high and sharp; QRS complexes, relatively low; T waves, flat.

Opinion: This graph was within normal limits for an infant.

SECOND EXAMINATION.—A second electrocardiogram, taken on October 10, when the infant was 3½ weeks of age (fig. 4), was reported on by Dr. Matthew Lewison as follows:

The auricular rate was 84; the ventricular rate, 84; the rhythm, sinus mechanism; the PR interval, 0.18 second; the QRS interval, 0.06 second. In lead I, the P waves were large and pointed; the PR interval was slightly prolonged for an infant of this age; the QRS complex spikes were upward and slurred;

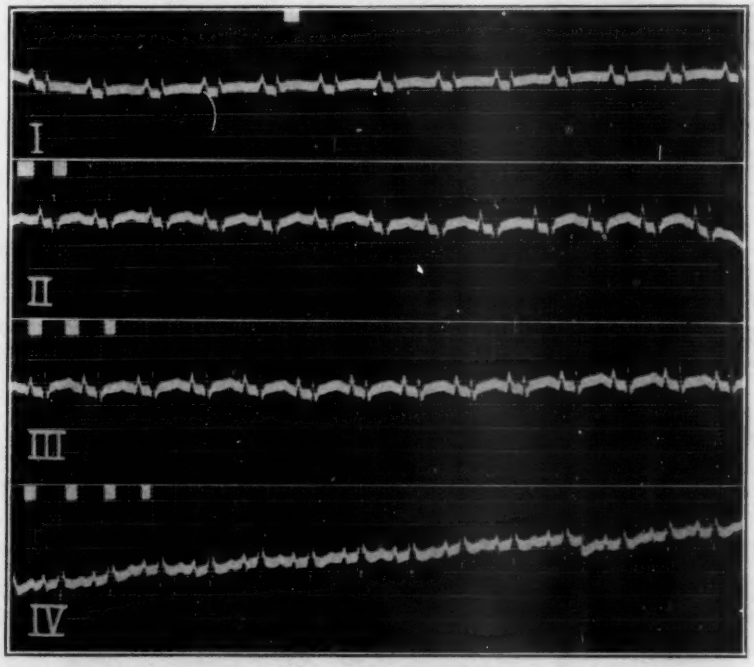

Fig. 4.—Electrocardiogram taken when the patient was 3½ weeks of age.

the T wave was isoelectric. In lead II, the findings were as in lead I except that an abnormal ST interval was present with the T wave. In lead III, the findings were as in lead II. In lead IV, the P wave was diphasic and the T waves were more pronounced.

Opinion: The rhythm showed a sinus mechanism; the P waves were unusually large and high in all leads; slight right axis deviation was present; the T wave in lead I was isoelectric; splinted QRS complexes were present in all leads, and the PR interval was prolonged.

THIRD EXAMINATION.—A third electrocardiogram and a stethocardiogram (sound tracing) were taken on November 10 (fig. 5), when the infant was 8 weeks of age. The findings as interpreted by Dr. Maximilian Kern were as follows:

The auricular rate was 105; the ventricular rate, 105; the rhythm, sinus mechanism; the PR interval, 0.2 second; the QRS interval, 0.06 second. In lead I, the P waves were large and sharp; the QRS complex, upright; the T wave, isoelectric. In lead II, the P wave was higher than in lead I; the QRS complex was upright; there was a small Q wave; the T wave was upright. In lead III, the P wave was upright; the QRS complex, upright, and the T wave, upright. Lead IV was less distinct in configuration than the other leads but was not unusual.

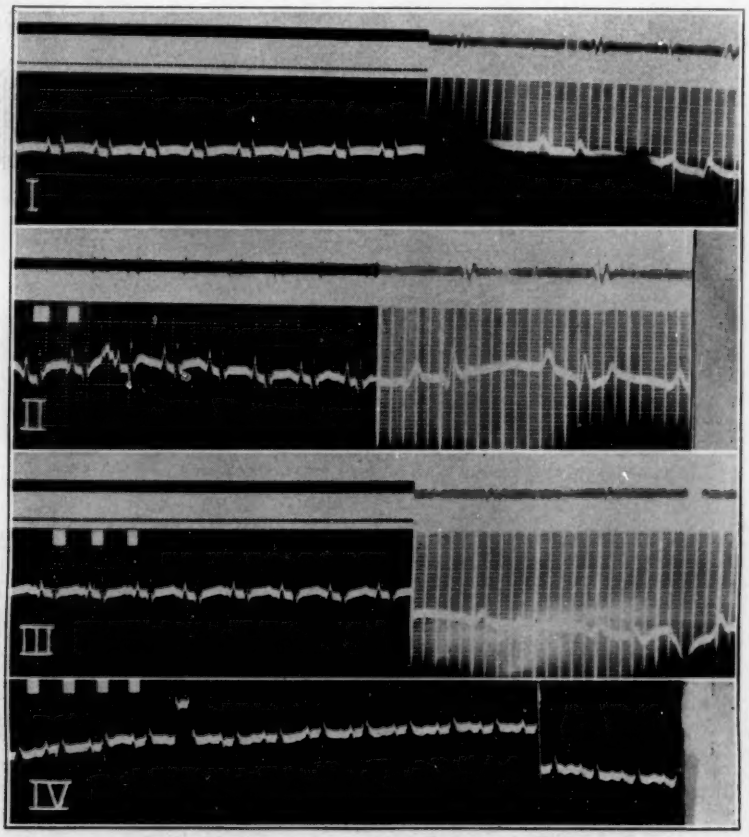

Fig. 5.—Electrocardiogram and sound tracings taken when the patient was 8 weeks old.

The sound tracings were interpreted as follows: In lead I, a presystolic murmur was noted at the apex area; in lead II, the presystolic murmur is more pronounced, and in lead III, a presystolic murmur is present. No sound tracing was made with lead IV.

Further Course.—On November 27, the infant began to have periods of cyanosis. She died suddenly on November 28, at the age of 2 months 13 days. An autopsy was performed by Dr. Aaron Gunther, assisted by Drs. Sidney Epstein and Edward Brophy.

Autopsy.—External Description: The body was that of a fairly well nourished white female infant. The weight was 3,178 Gm., the height, 47 cm. The skin was a pale grayish tan. The pupils were moderately dilated, round and equal, and the conjunctivas were pale purple gray. The nares contained a small amount of mucus. The ears were negative. The oral mucosa was dark purple gray, no teeth were present. The anterior fontanel measured 4 by 3 cm. The posterior fontanel was small. In the midline, extending from the xiphoid process to the umbilicus, there was a mass (measuring up to 7.5 by 6 by 5 cm.) on the anterior abdominal wall. In this mass intestinal loops, heart and undetermined viscera could be palpated. The finger nails were dark purple gray.

Abdomen: The midline fat measured up to 4 mm. in thickness. The so-called mass described on the abdomen was found to contain (1) the heart, (2) a portion of the liver, (3) the cecum, (4) the appendix, (5) the ileocecal valve and (6) the ileum. The pericardial sac was adherent both to the heart and to the skin immediately overlying it. The intestinal loops were moderately distended with gas. The abdomen contained a few cubic centimeters of clear straw-colored fluid. The diaphragm extended to the level of the fifth rib on each side; on the left side it was intact and on the right side it presented in its most medial anterior portion a defect up to 3 cm. in diameter through which the heart protruded.

Pleural Cavities: The left pleural cavity was free. The right pleural cavity contained, in addition to the lung, a large, dilated right auricle, which measured up to 4.5 cm. by 3 by 2.5 cm. All the structures of the heart below the auriculoventricular septum lay in the abdominal cavity, and that portion of the heart above the auriculoventricular septum was situated slightly lower than normal.

Heart: The heart was extremely elongated. The wall of the right ventricle measured up to 4 mm. in thickness; the wall of the left ventricle, up to 7 mm. The left ventricle was markedly dilated, the papillary muscles were markedly hypertrophied. The right ventricle was almost collapsed. There was a large septal defect, up to 15 mm. in diameter, which involved both the mitral and the tricuspid valve. In the proximal portion of the right ventricle, through a very small channel, a small pulmonary artery with a valve of three leaflets was given off. This pulmonary artery measured 7 mm. in circumference; it continued on, gradually narrowing, and divided into the right and the left pulmonary artery. The pulmonary artery lay somewhat to the left and posterior to the aorta throughout most of its course. The aorta measured 21 mm. in circumference; its intima was smooth. The bronchial arteries were dilated. The right auricle was extremely hypertrophied. The foramen ovale was widely patent and communicated with the left auricle, the wall of which also showed great hypertrophy. The wall of the right auricle measured up to 7 mm. in thickness; that of the left, up to 3 mm.

Lungs: Both lungs were crepitant to subcrepitant throughout. The pleura was smooth. The lungs on section were pale reddish gray and moderately dry. The bronchi contained a small amount of frothy thin material. The bronchial mucosa was pale purple gray. Hilar lymph nodes were inconspicuous.

Esophagus: The structure had a smooth, purple gray mucosa.

Spleen: The weight was normal. The organ was firm, with a thin capsule, and a smooth surface. On sectioning, follicles and trabeculae were distinct. At the hilus there was a very small accessory spleen, up to 3 mm. in diameter.

Intestines: The small intestine had a slightly thickened and edematous wall. The color was dark purple gray. The mucosa was purple gray to dark purple gray and was smooth and intact thruout. The mucosa of the large intestine was also purple gray.

Analysis of Cases Reported in the Literature

Reported by	Year	Anatomic Diagnosis				Sex			Gestational Age				Duration of Life						Comments
		Cervical	Thoracic	Abdominal	Combined Thoracic and Abdominal	Male	Female	Not Reported	Premature	Full Term	Not Reported	Stillborn	Less Than 24 Hours	1-7 Days	8-30 Days	1-12 Months	1 Year or More	Not Reported	
1. Haller	1706	..	+	..	..	+	..	..	..	..	+	..	12	..	..	..	..	..	
2. Vaubonnois	1712	..	+	..	..	..	..	+	+	..	..	+	..	..	..	..	..	..	
3. Prochaska	1734	..	..	+	..	..	..	+	..	..	+	+	..	..	..	..	..	..	Anencephalic
4. Herold	?	..	..	+	..	..	..	+	..	+	..	+	..	..	..	..	..	..	
5. Klein	?	..	..	+	..	+	..	..	+	..	..	..	..	..	..	..	..	+	
6. Pinelli	?	..	..	+	..	..	..	+	+	..	..	..	..	..	..	..	..	+	
7. Voigtel	?	..	..	+	..	..	..	+	+	..	..	..	..	..	..	..	..	+	
8. de Torres	1736	..	..	+	..	..	+	..	..	+	..	..	..	..	Several	..	..	..	
9. Breschet	1745	..	+	..	..	..	+	..	..	..	+	..	..	2.5	..	..	..	..	
10. Morand	1750	..	+	..	..	..	..	+	..	..	+	..	20	..	..	..	..	..	
11. Schulz	1763	..	+	..	..	+	..	..	..	..	+	..	5	..	..	..	..	..	
12. Sandifort	1773	..	..	..	+	..	+	..	..	..	+	..	..	1	..	..	..	..	
13. Ramel	1778	..	..	+	..	..	+	..	..	..	+	..	..	..	..	..	10	..	
14. Deschamps	?	..	..	+	..	+	..	..	..	..	+	..	..	..	..	..	Several	..	
15. Wilson	1798	..	..	+	..	..	..	+	..	+	..	..	..	7	..	..	..	..	
16. Fleischmann	1810	..	..	+	..	+	..	..	+	..	..	+	..	..	..	..	..	..	
17. Breschet	1826	+	..	..	..	..	+	..	..	..	+	..	Few	..	..	..	..	..	
18. Cruveilhier	1841	..	+	..	..	..	..	+	..	..	+	..	14	..	..	..	..	..	
19. Follin	1850	..	..	+	..	+	..	..	..	..	+	..	Few	..	..	..	..	..	
20. Jones	1855	..	+	..	..	+	..	..	+	..	..	..	13	..	..	..	..	..	
21. Danieli	1860	..	+	..	..	..	..	+	..	+	..	..	4	..	..	..	..	..	
22. O'Connor	1861	..	+	..	..	+	..	..	+	..	..	..	2	..	..	..	..	..	
23. Ranvier	1863	..	+	..	..	+	..	..	+	..	..	..	1	..	..	..	..	..	
24. Francois-Franck	1877	..	..	+	..	..	+	..	..	..	+	..	..	..	..	..	24	..	Pregnant
24. Tarnier *	1883	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	

25. Simpson	1882	..	+	..	..	..	..	+	+	..	..	+	..	..	..	..	..	..	.....
26. Huchard	1888	..	..	+	..	..	+	..	..	..	+	..	..	..	..	..	36	..	Four pregnancies
27. Braun-Fernwald	1894	..	+	..	..	..	..	+	..	..	+	..	..	1.5	..	..	..	..	.....
28. Holt	1897	..	..	+	..	+	..	..	..	+	..	..	..	..	..	5	..	..	.....
29. Barnardo	1897	..	+	..	..	..	+	..	+	..	..	..	6	..	..	..	..	..	.....
30. Abbott	1898	..	..	..	+	+	..	..	..	..	+	..	..	..	..	2	..	..	.....
31. Lilwall-Cormac	1903	..	+	..	..	..	+	..	..	+	..	..	..	1.12	..	..	..	..	Harelip
32. Matteucci	1903	..	+	..	..	+	..	..	+	..	..	..	..	2	..	..	..	..	.....
33. Goode	1903	..	+	..	..	..	+	..	..	+	..	..	..	..	16	..	..	..	.....
34. Wintsch	1906	..	..	+	..	+	..	..	..	+	..	..	..	2.12	..	..	..	..	Stomach and spleen also in sac
35. Ellis	1906	..	+	..	..	+	..	..	..	+	..	..	23	..	..	..	..	..	.....
36. Greiffenberg	1908	..	..	..	+	..	+	..	..	+	..	..	5	..	..	..	..	..	.....
37. Foy	1909	..	..	+	..	+	..	..	+	..	..	..	..	..	..	..	37	..	.....
38. Reiländer	1909	+	..	..	..	+	..	..	+	..	..	+	..	..	..	..	..	..	.....
39. Welch	1909	..	..	..	+	..	..	+	..	..	+	+	..	..	..	..	..	..	Heart ruptured during delivery
40. Kirmissen	1910	..	..	+	..	+	..	..	+	..	..	..	..	..	..	2	..	..	.....
41. Birnbaum	1912	..	+	..	..	+	..	..	+	..	..	+	..	..	..	..	..	..	.....
42. Holmes	1919	..	..	+	..	..	+	..	..	+	..	..	..	..	..	..	1.25	..	Died, streptococcic empyema
43. Torkomian	1922	..	+	..	..	+	..	..	..	+	..	..	..	..	..	..	3	..	Twin
44. Cosgrove and St. George	1924	..	+	..	..	+	..	..	+	..	..	+	..	..	..	..	..	..	Cleft palate and equinovarus
45. Cutler and Wilens	1925	..	+	..	..	+	..	..	..	+	..	..	..	3	..	..	..	..	Operated on
46. Greig	1926	..	+	..	..	+	..	..	..	+	..	..	..	..	..	..	1.08	..	.....
												..	..	..	8	..	..	..	Operated on; electrocardiogram reported
47. Bloch	1927	..	+	..	..	+	..	..	..	+	..								
48. Trillat et al	1934	..	+	..	..	..	+	..	+	..	..	..	..	1.25	..	..	..	..	.....
49. Ledényi	1935	..	+	..	..	..	..	+	..	..	+	+	..	..	..	..	..	..	.....
50. Kellett	1936	..	+	..	..	+	..	..	..	+	..	..	..	2	..	..	..	..	Electrocardiogram reported
												+	..	..	..	..	..	..	Hydrocephalus; equinovarus; spina bifida
51. Wanstrom	1936	..	+	..	..	+	..	..	+	..	..								
52. Barlow	1938	..	+	..	..	..	+	..	+	..	..	..	..	2.5	..	..	..	..	Electrocardiogram reported
Totals		2	28	18	4	25	14	13	19	16	17	11	13	11	3	3	8	3	

* Both men reported on the same case, Francois-Franck in 1877 and Harnier six years later.

Stomach and Duodenum: The mucosa was purple gray to dark purple gray and edematous. Bile could easily be expressed through the ampulla of Vater.

Pancreas: The weight was normal. The organ was firm, of a light gray tan color and uniformly lobulated. At the tail there were two accessory spleens.

Liver: The weight was normal. The anterior surface of the right lobe revealed a depression that corresponded to the area where the heart rested. The consistency was moderate; the capsule, thin; the surface, smooth. On sectioning, the surface was a pale brownish green to yellow tan. The acinar markings were indistinct.

Gallbladder: The mucosa was pale golden brown.

Adrenals: The weight was normal; the cortex was thin and pale yellowish tan; the medulla was reddish brown.

Kidneys: The weight was normal; each organ was firm, lobulated and dark purple gray, and the capsule stripped with ease. The cortex measured up to 3 mm. in thickness, and the markings were distinct.

Genitalia: The uterus appeared normal in size and shape. The fallopian tubes were small and convoluted. The fimbriated ends were patent. Both ovaries were large and contained cysts up to 1 cm. in diameter, filled with clear straw-colored fluid.

Anatomic Diagnoses: The following conditions were present: ventral hernia of the abdominal wall; ectopia cordis abdominalis; diaphragmatic hernia at the foramen of Morgagni (junction of the sternal and the costal portion of the diaphragm); protrusion of the heart through the diaphragmatic hernia into the ventral hernia on the abdominal wall; marked elongation of the heart; chronic passive congestion of the liver, spleen and kidneys; multiple (three) accessory spleens; catarrhal stasis of the alimentary tract; multiple follicular cysts of both ovaries; fibrous obliteration of the pericardial sac.

An examination of the heart was made by the anatomist Dr. Harry Sicher. His anatomic diagnosis on that organ was as follows:

"The vena cava enters the right atrium in normal position; no right atrioventricular opening is present; the foramen ovale is patent; the left atrium receives a rather large pulmonary vein; the left atrioventricular opening is normal; there is no sign of a tricuspid valve; the bicuspid valve is normal, with normal papillary muscles; the right ventricle is common with the left through a wide intraventricular foramen. The right ventricle is normal in position but very small; the aorta and pulmonary arteries arise in normal position from the left and right ventricles respectively. The pulmonary artery is very small; the semilunar valves are otherwise normal. There is no trace of a ductus arteriosus; there are three rather large bronchial arteries, one arising from the aorta and two from the first two intercostal arteries."

Dr. Sicher offered the following explanation for this unusual embryologic defect:

"The primary malformation is a displacement of the common atrioventricular opening. This opening did not shift to the right side. Therefore, the developing atrial septum hit not the middle but the right border of the atrioventricular opening, and instead of the common atrioventricular opening being divided into a right and a left one, the right atrium was shut off from the ventricle altogether. As a consequence: (*a*) No tricuspid valve developed; (*b*) the foramen ovale remained patent; (*c*) the left ventricle alone received blood, and (*d*) the right ventricle received only a small amount of blood through the intraventricular foramen. Most of the blood was thrown out through the aorta, and very little

blood went through the pulmonary artery. This accounts for the hypoplasia of the pulmonary artery and for the very early obliteration and disappearance of the ductus arteriosus, because no necessity arose of shunting blood from the pulmonary artery to the aorta."

COMMENT AND REVIEW OF THE LITERATURE

We have been able to find 52 cases of ectopia cordis in the literature, as shown in the table and in the bibliography.[1] This condition has been defined by Maude Abbott as "a displacement so that the heart passes out of the thorax and comes to lie either upon the outer surface of the body or in the abdominal cavity." It was first described by Haller in 1706. Weese, in 1818, classified ectopia cordis into three types: ectopia cordis cum sterni fissura, ectopia suprathoracica and ectopia subthoracica. Townsend (1833), Todd (1836-1839) and Rauchfuss (1878) preferred the following terms: cervical heart (the organ lies high up in the neck); pectoral heart with fissure of the sternum, and abdominal heart (the organ has passed through a defect in the diaphragm and into the abdominal cavity).

Although life in the presence of ectopia cordis is usually short, a number of patients have been seen in whom the condition was present in adult life. Kellett in 1936 stated that the average duration of life was thirty-six hours. Many of the patients he reported on were still-born; others were born prematurely and lived a few hours. In his series the longest duration of life was eight days. Our review, however, disclosed 12 patients whose length of life exceeded this.

Two observers, Francois-Franck in 1877 and Tarnier in 1883, reported the occurrence of ectopia in a woman aged 24 when first seen. She had, in addition, a large intestinal eventration to the level of the umbilicus. She was seen during pregnancy at the age of 35 by Tarnier, who recorded that the sternum was bifid distally and that the atria could be felt only by pushing the finger up into the sternal cleft. Breschet, who in 1826 published an excellent review of this subject, cited the case reported by Ramel in 1778, that of a girl of 10 years whose heart was in the epigastrium. The heart could be grasped and its movements felt to synchronize with the pulse. Breschet also reported on the famous case observed by Deschamps. Deschamps recorded the postmortem examination of an old soldier who, after having been in several campaigns, died of suppurative nephritis (right kidney). He stated: "The left kidney was absent and in its position lay the heart in its membrane, the vessels passing through a hole in a normal diaphragm and into the thorax." Huchard in 1888 reported a case of abdominal ectopia cordis in a 36 year old woman who had had four pregnancies. The whole heart occupied the epigastric region and could be grasped in the hand.

1. The reports are cited chronologically in the table. In the bibliography the authors' names are arranged alphabetically, to facilitate reference.

Caudad to it was a defect of the midline of the abdomen with a ventral hernia. He did not specify whether there was a cleft sternum. During this woman's last pregnancy, Huchard stated that she had fainting spells, with a small irregular pulse. He interpreted this as indicating "a congenital defect of the heart or some embarrassment of its action."

Holt in 1897 reported on a 5 month old boy in whom an umbilical hernia at birth was noted to contain a hard pulsating mass. The child was above the average weight at birth and had some cyanosis during the first week of life. The rectus abdominis muscles were widely separated above the umbilicus, and at the center of the protrusion a circular area 2 inches (5 cm.) in diameter was covered only by a membrane, at the lower edge of which was the umbilicus. A finger could be passed under the heart and its apex raised. A loud systolic murmur was heard all over the heart, but most distinctly at the left of the xiphoid process. Torkomian in 1922 described a 3 year old boy, the second of twins, in whom the heart protruded through an incomplete sternum, the skin over the deficiency being thin and transparent. He made the statement that this degree of ectopia is not incompatible with health and mentioned that Ramire, of Mexico, in 1867 reported a case of ectopia cordis in a man aged 75.

Greig reviewed the literature of ectopia cordis thoroughly in 1926. He found 19 cases with and 19 cases without a cleft sternum. In the latter group there were 2 cases of cervical, 4 of thoracic and 13 of abdominal ectopia cordis. Our review of the literature disclosed 14 cases in addition to those previously reported by Greig. Of these, only one was of the abdominal type. This patient reported on by Holmes in 1919 lived fifteen months and died of empyema following a hemolytic streptococcus pneumonia. Goode in 1903 reported an interesting and unusual case. A female infant weighing 5½ pounds (2,495 Gm.) was born with the manubrium intact but the remainder of the sternum absent. The ectopic heart was anointed with oil and covered with a pasteboard cone. The child lived sixteen days.

Ectopia cordis as reported in the literature occurred in 25 males and in 14 females. In 13 instances the patient's sex was not recorded. Many of the infants were stillborn, and several were prematurely born, as shown in the table. In most instances the delivery was normal. In Welch's case (1909) the heart ruptured during delivery. In many cases, extensive malformations of the heart and of the great vessels coexisted. In the series reported by Greig there were 2 trilocular and 3 bilocular hearts, 6 with two superior venae cavae and 4 with multiple cardiac anomalies. Of the three types of ectopia cordis, the cervical appears to be incompatible with life. The thoracic offers a better prognosis, and with the abdominal type a number of patients have lived well into adult life.

The genesis of ectopia cordis has not been fully explained, although several hypotheses have been offered. It has been suggested that it may be due to a defect in the midline closure of the body walls of the embryo. A second suggestion is that in thoracic and in abdominal ectopia early derangement of the vascular mesocardium may bring about improper fixation of the heart and be a factor in its displacement.[2]

Electrocardiographic studies of ectopic hearts have been reported in 3 cases. Bloch's only comment on her case (1927) was that the electrocardiogram showed a normal rate, of 130 to 140 beats per minute. Kellett (1936) made a series of tracings in his case, employing lead II and leads directly from the heart and using nonpolarizing electrodes. He found that when cold was applied to the surface of the ventricles there was a change in deflexions. The tracings that Barlow (1938) made in his case showed that the conduction mechanism directly through the heart was normal but that conduction through the body was impaired; no deflections were obtained with conventional leads.

Surgical correction has been attempted in 2 cases (Cutler and Wilens, 1925; Bloch, 1927). In both instances the heart was restored to the thoracic cavity and covered with skin flaps, but the sutures had to be released immediately because of the rapid embarrassment of the heart action. On the basis of the review of the literature, it would seem that patients with ectopia cordis abdominalis do better if managed without surgical intervention.

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CYSTIC FIBROSIS OF THE PANCREAS

REPORT OF A CASE, WITH CLINICAL AND PATHOLOGIC OBSERVATIONS

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Andersen,[1] in 1938, gave a comprehensive analysis of the clinical laboratory and pathologic aspects of cystic fibrosis of the pancreas, basing her report on a series of 49 cases of the disease gathered from the files of the Babies Hospital in New York and from recent and past pediatric literature. Since then further cases have been recorded by her and by others. The following report describes another instance of the disease in which the diagnosis was proved by postmortem observations.

REPORT OF CASE

C. H. Jr., aged 7 months, was brought to the office of one of us (L. R.) for examination on April 24, 1941, because of "eighteen movements over the past three days," because of failure to gain and because of a severe cough not amenable to treatment.

Pregnancy and Birth History.—The mother, a primipara, had an uneventful first, full term pregnancy. She delivered a 6 pound (2,722 Gm.) baby spontaneously and without complication. However, in order to avoid a large baby, she had restricted herself in fats and carbohydrates. She had avoided, as much as possible, animal and vegetable fats, skimming her daily 24 ounces (700 cc.) of milk and eating neither butter nor eggs. She had eaten freely of lean meats, raw and cooked vegetables, and fresh and stewed fruits. She had sparingly eaten bread, potatoes and puddings. She had not fortified her diet with any of the commercially obtainable vitamins.

Family History.—The mother was 20 years of age, and the father, 22, at the time of the infant's birth. There was no past or present evidence of chronic illness and no present acute illness in either parent. Both the maternal and the paternal grandparents were alive and well.

Feeding History.—The infant had been completely breast fed for its first three months, but diarrhea occurred continually from the first day. "At least sixteen green and watery movements were passed during the first twenty-four hours." During the three month period the stools continued to be loose and green, aver-

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1. Andersen, D. H.: Cystic Fibrosis of Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**:344 (Aug.) 1938. For a complete bibliography the reader is referred to Dr. Andersen's paper.

aging five in number daily. No special attempts had been made to control the diarrhea. The gain was slow. At the fourth month the infant was removed from the breast and fed as follows:

1. Whole unboiled cow's milk, water and dextrimaltose mixtures, of varying proportions, were used for three weeks. The stools continued to number four to six daily. They were bulky and mushy rather than loose. Their odor now became offensive. There was no vomiting. The average weekly gain was about 3 ounces (85 Gm.).
2. Evaporated goat's milk, water and dextrimaltose, in varying proportions, were then given for two weeks, without improvement in the number and character of the stools or in the weight gain.
3. Whole grade B milk, unboiled, with water dilutions and added dextrimaltose, was tried for two weeks without improvement.
4. Pectin-agar, dextrimaltose and water mixtures, proportions not known, were given for one month. Diarrhea was unimproved and weight was stationary.
5. The formula on the date of observation was: water, 32 ounces (946 cc.); powdered protein milk, 12 tablespoonfuls; corn syrup (blue label Karo), 1 tablespoonful. Eight ounces (236 cc.) was given every four hours, four feedings daily. Also were given two bananas daily, Jello, calves' liver, tomato juice, 20 drops of a cod liver oil concentrate, and 10 drops of a vitamin B complex concentrate.[2] With this regimen the stools were at times dry and at others mushy and frothy. They were extremely large and foul smelling and numbered about five daily. The child's appetite was good.

The foregoing changes in diet were made under the guidance of a number of different physicians.

Past History.—At 5 months the infant had a cold manifested by a continual cough unresponsive to medicine and to "cold vaccine" given daily for six days.

Physical Examination.—The infant was well formed but somewhat poorly nourished. The circumference of the head was 37.5 cm., of the chest 40 cm. and of the abdomen 69 cm.; the length was 40 cm. The anterior fontanel was 2.5 by 2.5 cm. and was depressed. The weight was about 5,900 Gm. (13 pounds). The pupils were equal and reacted to light. The ear drums were physiologic. There was a mild nasopharyngitis. The tongue was moist and clear. The throat was normal. The chest was well formed and breathing regular but somewhat effortful. There were numerous coarse and fine rales over the anterior and posterior parts of the chest and a moderate sternal retraction on inspiration. A moist cough persisted at intervals. The heart was not enlarged. The abdomen was markedly distended and tympanitic. The liver was palpable at the ribs' margin; the spleen could not be felt. There were no abdominal masses or areas of tenderness. The superficial lymph nodes were not palpable. The deep reflexes and the superficial abdominal and cremasteric reflexes were easily elicited. Skin turgor was good, but the panniculus was thin. The child had been circumcised.

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2. The cod liver oil concentrate used, according to the manufacturer, each drop, or ½ minim (0.031 cc.), contains not less than 1,560 U. S. P. units of vitamin A and 156 U. S. P. units of vitamin D per drop (½ minim [0.03 cc.]). The vitamin B complex concentrate was a liquid each drop of which contains approximately 32 international units of vitamin B_1, 15 micrograms of riboflavin and, in addition, very small amounts of all other natural B complex factors as derived from rice bran.

The infant was suspected of a possible pancreatic syndrome because, first, of its celiac or chronic intestinal type of indigestion with bulky, foul-smelling stools, varying in consistency from a froth to a mush; second, of its failure to gain weight despite a good appetite; and, third, of the complicating infection of the respiratory tract.

Because of the history of poor response to various milk formulas, the patient was put on a regimen consisting of 4 tablespoonfuls of banana powder to 8 ounces (237 cc.) of sterile water, fed at four hour intervals. He was also given 3 tablespoonfuls of creamed very ripe banana at each feeding, 4 ounces (118 cc.) of orange juice daily, 4 drops of percomorph liver oil (about 1,330 U. S. P. units of vitamin A and 185 U. S. P. units of vitamin D per drop) three times daily and 20 drops of carotene in cottonseed oil (yielding approximately 500 U. S. P. units of vitamin A per drop) three times daily. Within twenty-four hours the stools formed and the number decreased to three daily, but each movement was dry and extremely bulky. The appetite was eager. After the child had had formed stools for forty-eight hours, 2 tablespoonfuls of pot cheese (a nearly fat-free cottage cheese), 1 tablespoonful of boiled white rice, 1 tablespoonful of strained vegetable and 1 tablespoonful of unsweetened apple sauce were consecutively added to each feeding on successive days, without digestive upset. The amounts of these foods were increased gradually, except in the case of pot cheese. The stools continued to be well formed but bulky, and the number remained at one to three daily. On May 2 the patient's weight had increased 12 ounces (340 Gm.).

However, the respiratory distress was increasingly worse. After three weeks of observation, a spasmodic cough, simulating that of whooping cough, developed. Many fine rales were distributed over both lungs, with exaggeration at both bases posteriorly. The breathing was extremely labored; the sternal and chest wall retractions on inspiration were marked. There were brief periods of cyanosis during the coughing spasms. There was no fever.

Because of the family's distaste for hospitalization an oxygen tent was instituted in the home and continuous nursing care given. Under oxygen the spasmodic breathing attacks were at first greatly reduced in number and severity. The digestion and appetite continued good. Epinephrine hydrochloride, atropine sulfate, and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) were administered but had questionable value in minimizing the paroxysms or the bronchopneumonic infection.

On June 1, about one month from the beginning of observation, the temperature rose to 101 F., rectally. On account of the increasingly greater respiratory difficulty, of the cyanosis and of the sudden apparent loss in weight, hospitalization was advised and agreed to.

Course in Hospital.—The infant continued to take his feedings well for the first two days of stay in the hospital. The temperature fluctuated between the admission point of 98 F. rectally, and the terminal point of 104 F., on June 4, the fourth day of admission. Cyanosis and difficult breathing were progressively worse. A mucopurulent and hemorrhagic discharge from the nose and throat persisted. The spasmodic attacks now occurred continually, every minute or oftener. Phenobarbital, codeine, atropine, epinephrine and oxygen were ineffectual. On the third day abdominal distention was extreme, although there was little variation in the character of the stools. Appetite ceased on this day, and the child could not be forced to take food. He became comatose, and death occurred ninety-six hours after his admission.

Laboratory Data.—The leukocytes numbered 21,500, with 50 per cent neutrophils, 47 per cent lymphocytes, 1 per cent lymphoblasts and 2 per cent myelocytes; the erythrocytes numbered 4,070,000; the nuclear index was 2 per cent, and there was a marked shift to the left. The hemoglobin content was 52 per cent (8.9 Gm.) per hundred cubic centimeters; the color index, 0.6. Smears of the mucopurulent discharge from the nose and throat showed staphylococci (Staphylococcus albus) and a few streptococci. The culture of this discharge revealed alpha prime streptoccocci. The Neufeld reaction for pneumococci of types I to XXXII was negative. The urine was yellow, clear and faintly acid. Tests for albumin, sugar, acetone and diabetic acid gave negative results. There were no casts. About 0 to 1 leukocyte and 0 to 1 erythrocyte per high power field were counted.

Roentgenologic Picture.—General infiltration was evidenced by the coarse mottled appearance throughout the left lung and the upper portion of the right lung. The decreased irradiability is characteristic of bronchopneumonia.

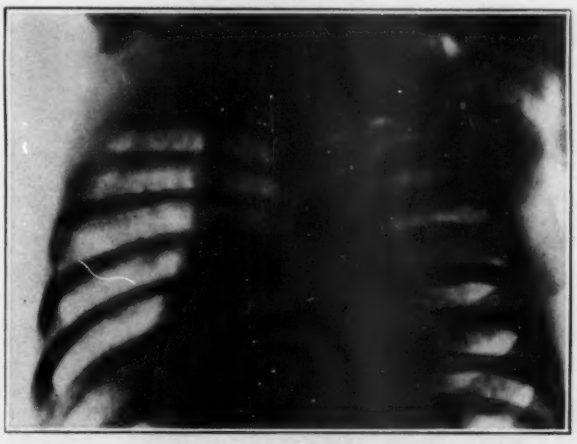

Fig. 1.—Roentgenogram indicating mottling characteristic of bronchopneumonia.

Gross Examination at Autopsy.—The body was that of a rather well developed but poorly nourished boy approximately 8 months of age. There was no evidence of emaciation or of muscular atrophy. The abdomen was greatly distended. There was a slight degree of rectal prolapse. A yellowish green mucopurulent exudate came from both the mouth and the nose. The pupils were equal and the scleras clear. The lips and the fingers were cyanosed. The adipose tissue of the abdomen measured 0.4 cm. in thickness. The intestines were distended. The margin of the liver extended 2.5 cm. below the costal margin. The transverse diameter of the heart was 6 cm., the transverse diameter of the chest, 14 cm. The chest was well formed and elliptic on section.

Lungs: The right pleural cavity showed a moderate degree of fibrinous pleurisy. The bronchi were slightly congested and contained a greenish yellow mucopurulent exudate. On section of the right lungs the bronchi and bronchioles exuded a similar mucopurulent exudate. There were numerous abscesses throughout the lung tissue. Patchy pneumonic areas were found scattered throughout both lungs. There was some congestion of the lower lobes, and the lungs floated.

Thymus: The thymus was normal and weighed 12 Gm.

Thyroid, Larynx and Esophagus: These structures were all normal.

Heart: The heart weighed 47 Gm. The pericardial surfaces were glistening; a few milk spots appeared on the visceral pericardium. There was no increase of pericardial fluid. No great abnormalities of the heart were noted. The musculature was of good coloration. The foramen ovale and the ductus arteriosus were closed. The aorta and the valves showed no pathologic change.

Peritoneal Cavity: The stomach and the intestines were distended, with consequent thinning of the walls. There was a moderate increase of clear yellow peritoneal fluid. The pylorus showed no pathologic change.

Lymph Nodes: The mesenteric and the tracheobronchial lymph nodes were enlarged, the largest measuring 1.5 cm. in length.

Liver and Gallbladder: The liver was enlarged, weighing 290 Gm. It was yellowish brown and had a smooth surface and a fatty consistency. The gallbladder contained a small amount of dark bile.

Fig. 2.—Photomicrograph of the pancreas, showing irregularly shaped and dilated acini lined by cuboidal epithelium. Between the acini are broad strands of connective tissue with foci of lymphocytes. The islands of Langerhans are preserved and somewhat larger than normal. Hematoxylin and eosin; × 150.

Appendix: The appendix was normal.

Spleen: The spleen measured 5.5 by 3.5 cm. and was congested. The weight was 15 Gm.

Pancreas: The pancreas was normal in size, but was of rather firm and gritty consistency. It was impossible to dissect out the ducts.

Genitourinary Tract: The kidneys appeared normal. The ureters were normal in their course and were not obstructed. The urinary bladder contained a small amount of clear urine.

Adrenals: The adrenal glands were normal.

Testicles and Adnexa: The testicles and adnexa were normal.

Microscopic Examination.—Pancreas: The pancreatic acini were distorted and contained concretions of various sizes, and the acinar cells were flattened to form a thin epithelial wall around them. Some of the acini and small ducts were cystic and contained large pink-staining concretions. It was difficult to distinguish the small ducts from acini in some areas. Some metaplasia was noted in the acini containing the large concretions. The smaller concretions were homogeneous, while the larger ones were laminated. Surrounding the acini and lobules there were varying amounts of fibrous tissue which were diffusely infiltrated with lymphocytes and plasma cells. The islands of Langerhans were normal in number and appearance. A small amount of fatty tissue was found in the fibrous areas.

Spleen: The spleen was congested, and the malpighian corpuscles were small and widely separated. A small number of polymorphonuclear leukocytes were found in the pulp.

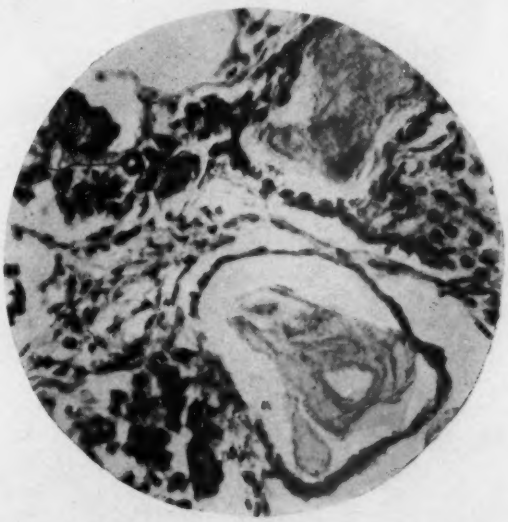

Fig. 3.—Photomicrograph of the pancreas, showing dilated lumens containing an amorphous pink-staining material. Hematoxylin and eosin; × 250.

Stomach and Intestines: The stomach and intestines showed no abnormality except for a moderate infiltration of plasma cells and lymphocytes in the submucosa.

Liver: The liver cells contained a large amount of fat, and there was a slight increase of fibrous tissue in the portal area.

Lymph Nodes: The mesenteric and bronchial lymph nodes showed hyperplasia.

Kidneys: The kidneys showed cloudy swelling of the tubules.

Heart: The heart showed no abnormality.

Lungs: The bronchi showed bronchitis and peribronchitis in all the sections. The bronchial lumens were filled with a purulent exudate, and the alveoli showed patchy lobular pneumonia with scattered areas of air-bearing tissue. There were congestion and terminal edema throughout. In the abscessed areas, numerous bacteria were seen. In some areas the epithelium of the bronchi was composed of more cell layers than usual, evidencing squamous metaplasia of the superficial

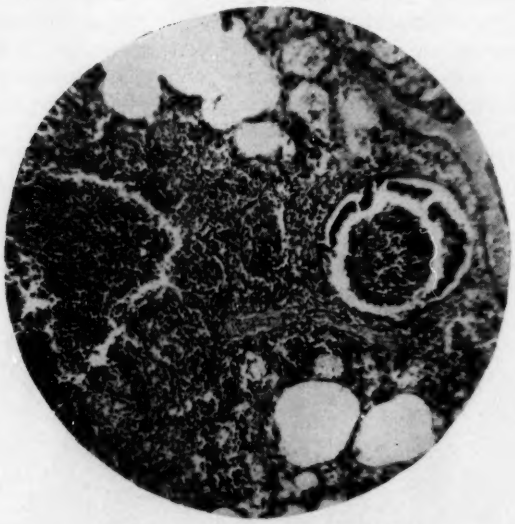

Fig. 4.—Photomicrograph of a lung, showing bronchiolectasis, bronchopneumonia and abscess. Hematoxylin and eosin; × 150.

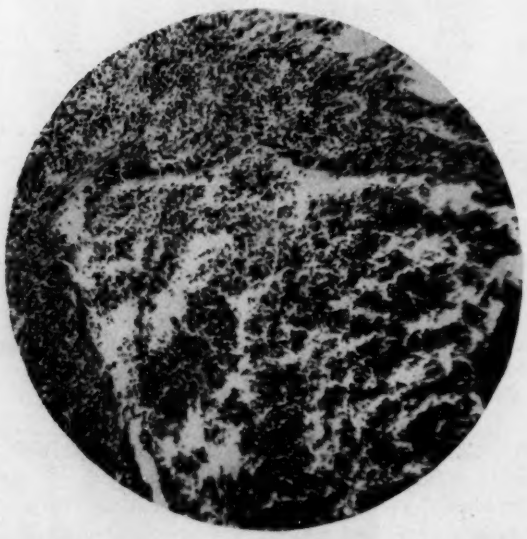

Fig. 5.—Photomicrograph of a bronchus distended with purulent exudate, with infiltration of surrounding lung tissue. Hematoxylin and eosin; × 150.

Fig. 6.—Photomicrograph of a bronchus, showing epithelial metaplasia with lymphocytic cell infiltration of the stroma. Hematoxylin and eosin; × 150.

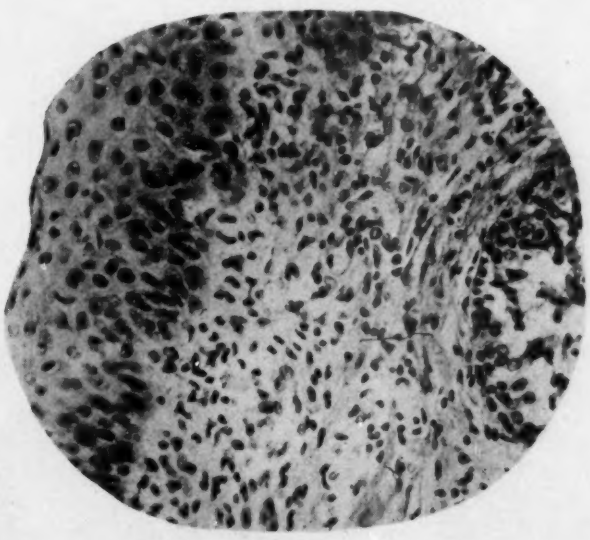

Fig. 7.—Photomicrograph of a bronchus, showing epithelial metaplasia replacing the ciliated pseudostratified columnar epithelium usually present in the respiratory tract. Hematoxylin and eosin; × 250.

layers. The submucosa was diffusely infiltrated with numerous lymphocytes. The epithelium of the trachea was slightly thickened, and there was metaplasia of the lining epithelium. The vocal cords showed no pathologic change except edema.

The thymus, thyroid, esophagus, gallbladder, adrenals and testicles appeared normal.

Cultures of material removed from the lung post mortem were negative for pneumococci; some alpha prime streptococci and staphylococci (Staph. albus) were found.

Anatomic Diagnoses: The diagnoses were cystic fibrosis of the pancreas, tracheitis, bronchitis, acute bronchiolitis, bilateral focal pneumonia with abscess formation, and fatty changes of the liver.

COMMENT

Crystallization of a symptom complex diagnostic of cystic fibrosis of the pancreas cannot be said to have been perfected. However, such a disease must be primarily considered if in an infant between birth and the age of 6 months celiac symptoms occur either alone or complicated by a progressive infection of the respiratory tract with a paroxysmal cough simulating that of pertussis. In the foregoing case the diagnosis rested on the presence of such a symptom complex and was verified by post-mortem observations. The instances in which the condition occurs during the newborn period and is associated, as Andersen has emphasized, with such congenital malformations as atresia of various portions of the small intestine, Meckel's diverticulum, atresia of the cystic duct and congenital malformation of the heart, are only academically problematic, because of early fatality. In infants over 6 months and in children from 1 to 15 years, especially when without infection of the respiratory tract, cystic fibrosis of the pancreas may be indistinguishable from, and is most often diagnosed as, celiac disease.

Diagnosis can be fortified by examination of the duodenal contents for pancreatic enzymes. Absence, or a functionally deficient amount of, these enzymes, Andersen's investigations show, determines the nature of the disease. Completely diagnostic of cystic fibrosis of the pancreas as described in the instance given is the association of the celioid symptoms with absence or a functionally deficient amount of trypsin in the pancreatic secretion.

From a clinical point of view we have found it convenient to classify patients with the celioid, or chronic intestinal, type of indigestion as follows:

A. Patients with suspected organic changes in the pancreas.

1. Those with starch indigestion, having large, frothy or mushy, sour-smelling stools and responding best to a diet high in protein, normal or moderately low in fat, and low in starch and in dextrin.
2. Those essentially with fat indigestion, having large, loose, pale yellow or grayish white, foul-smelling stools with plainly undigested neutral

fat, and responding best to a diet low in fat. Infection of the respiratory tract is a common development.

3. Those with protein indigestion, having large, bulky stools, which are at times firm and at other times mushy and which have a foul, putrefactive odor. The patients with this type of indigestion most often have respiratory complications. They respond best to a low protein diet with the addition of pancreatin to the feedings.
4. Those with a mixed type of indigestion, whose stools are at times characteristic of starch and at other times of fat or protein indigestion. This group presents a most difficult feeding problem.

B. Patients without suspected organic changes in the pancreas.
All these are patients with a true celiac syndrome, responding chiefly to banana feedings.

The infants in whom starch indigestion prevails most likely have no amylopsin or have a functionally deficient amount of it. However, this enzyme is normally absent in the duodenal contents of infants from birth to about the age of 4 months. When thick feedings, as for pylorospasm or pyloric stenosis, are employed, one does not, however, usually encounter evidence of celioid indigestion. The stools are as a rule well digested over a period of five to six weeks. The thick feedings cannot be considered as offering merely a mechanical bolus for overcoming pyloric muscular thickening or spasm. Consequently, absence of amylopsin from the duodenal contents, we believe, cannot in itself explain celioid indigestion. Those infants showing a high content of neutral fat in the stool should have a correlating low content of lipase in the duodenal juice, and those with protein indigestion should have a low level of trypsin. In those instances in which no pattern in diet can be closely followed with good therapeutic effect, absence of all pancreatic enzymes in the duodenum should be expected. However, we have made no investigation to substantiate the supposed correlations between the type of indigestion and the type of deficiency of the pancreatic enzyme or enzymes.

In the true celiac syndrome a functional digestive disturbance is suspected. The stools usually contain a high percentage of split fat, and, according to Andersen, the duodenal pancreatic enzymes are normal. Eventual complete cure in this group is the rule. We made no study of the vitamin A content of the blood in our case; but the mother's diet during pregnancy is indicative of a vitamin A deficiency. However, examination of the patient's blood for lowered vitamin A content, examination of the stool for neutral and split fat, determination of the blood cholesterol level and making of sugar tolerance curves are only of questionable diagnostic value. Response to diet, too, is not conclusive, since, as Andersen has shown, a child with chronic intestinal indigestion responding to a celiac disease regimen proved post mortem to have cystic fibrosis of the pancreas. Nevertheless, most patients, especially those in

the age groups over 6 months, progressively improving under a celiac disease regimen and suffering no typical respiratory complications are likely not to have cystic fibrosis of the pancreas.

Loose diarrhea with complicating bronchopneumonia need not be confused with celioid types of disease, because of the absence of chronicity and because of the difference in feeding response. Lipid pneumonia with diarrhea is to be considered in the differential diagnosis. Focal infections, especially acute otitis media, with parenteral diarrhea can be eliminated both by the history and by the discovery of the focus or foci of infection. In these disturbances the duodenal contents, when study is possible, will show no perversion of pancreatic enzyme secretory function.

SUMMARY

A case of cystic fibrosis of the pancreas in which the diagnosis was made clinically and proved by autopsy is described, and the postmortem observations are given. A classification of chronic intestinal indigestion, chiefly from a clinical point of view and on the basis of response to therapy, is presented.

ISOLATED SEGMENT OF INTESTINE ASSOCIATED WITH DUODENAL ATRESIA

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LOS ANGELES

Although the anomaly of duodenal atresia alone is comparatively rare in the newborn, it has been described so frequently and so thoroughly that the presentation of a single case would not be justified. The complication of duodenal atresia by an additional rare anomaly of the intestine, however, is worthy of record.

REPORT OF A CASE

The patient was a newborn girl delivered on Feb. 15, 1941. The mother was admitted to the hospital during the eighth month of an uneventful pregnancy, with ruptured membranes. Her labor was rapid, and delivery was uncomplicated. The postpartum course was satisfactory.

At birth the infant weighed 2,370 Gm. and measured 46 cm. in length. Its condition immediately after birth presented nothing unusual. Approximately 24 hours after birth regurgitation of both fluids and food was noted, which was almost immediately followed by persistent projectile vomiting. The vomitus was bile stained and was considerably greater in quantity than the amount of fluid and food ingested. Abdominal distention was pronounced, especially in the upper half of the abdomen. After the introduction of a stomach tube, considerable bile-stained fluid was recovered. There was almost immediate relief of the distention, so that the abdomen became scaphoid and flaccid. Palpation of the abdomen at this time revealed a wormlike mass in the right lower quadrant. This mass was firm and freely movable from one side of the abdomen to the other.

About twelve hours after the onset of symptoms, dehydration was extreme and was not lessened by parenteral administration of fluids. During the first twelve hours after delivery there was a single acholic stool, but afterward there was a complete absence of stools. The child's temperature varied between 98.6 and 100 F. degrees for the first two days and then rose to 104.6 F. The baby died three days after birth, with a clinical diagnosis of duodenal atresia associated with an unclassified intestinal anomaly.

Gross Postmortem Examination.—The body was that of a 3 day old infant weighing 1,810 Gm. and 46 cm. in length. The chief pathologic changes were located in the abdominal cavity, particularly in the gastrointestinal tract.

The esophagus was dilated to approximately three or four times the normal size for an infant of this age. The duodenum was extremely dilated and was so

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distorted that the second and third portions could be differentiated only with difficulty. The duodenum terminated abruptly in a blunt blind pouch. The stomach and duodenum contained considerable soft food material. The walls of both the duodenum and the stomach were slightly thickened.

Immediately beyond the blind pouch of the duodenum there occurred a gap, after which the intestine continued, starting from another blind pouch and running onward as small bowel in a fairly regular fashion as far as the cecum, which was situated in approximately its normal position. The small intestine as far as the ileocecal valve, exclusive of the duodenum, measured 34 cm. in length. From the terminal portion of the small intestine the cecum arose, and from it in turn an

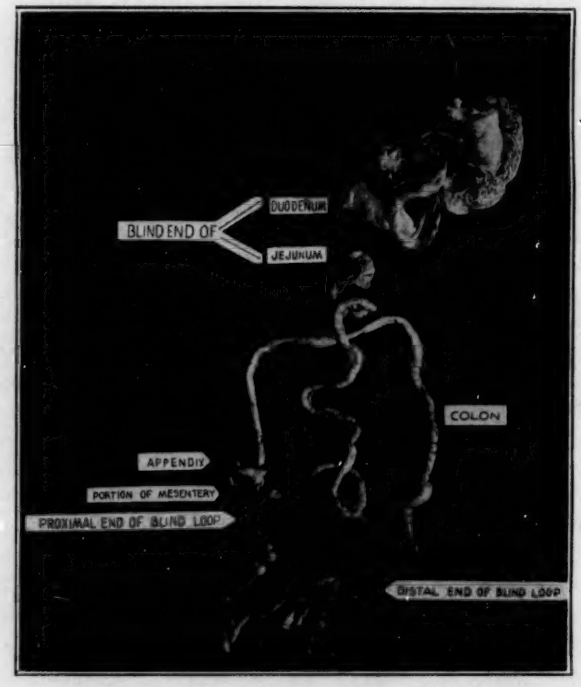

Fig. 1.—The intestine.

appendix measuring 3 cm. in length was clearly evident. The large bowel did not appear unusual and measured 30 cm. in length. The intestinal tract beyond the duodenum and as far as the rectum was completely collapsed, practically empty and entirely free from evidence of bile pigment.

After the portion of intestine just described had been dissected free, there remained in the right lower quadrant a segment of intestine which measured 45 cm. in length. The distal end of this segment was rather thick and dilated, measuring approximately 2 cm. in diameter. On cut section it was found to contain greenish material which chemically gave a negative reaction for both bile and urobilinogen. From the distended distal end this free segment narrowed very

gradually until it reached a point 5 cm. from the proximal end. Here its diameter rapidly became very narrow and its structure cordlike for a distance of 4 cm., finally terminating in a cystlike structure 1 cm. in diameter.

The spleen and the liver were not unusual. The renal cortices appeared normal, but in the projections of the papillae there were distinct bright yellow markings, pointing toward the pelvis. The heart and the lungs were normal. The head, neck and extremities did not reveal any other abnormalities.

Microscopic Postmortem Examination.—Three blocks of intestine were taken to compare the histologic picture of the isolated segment with that of the known sections of ileum and colon as controls.

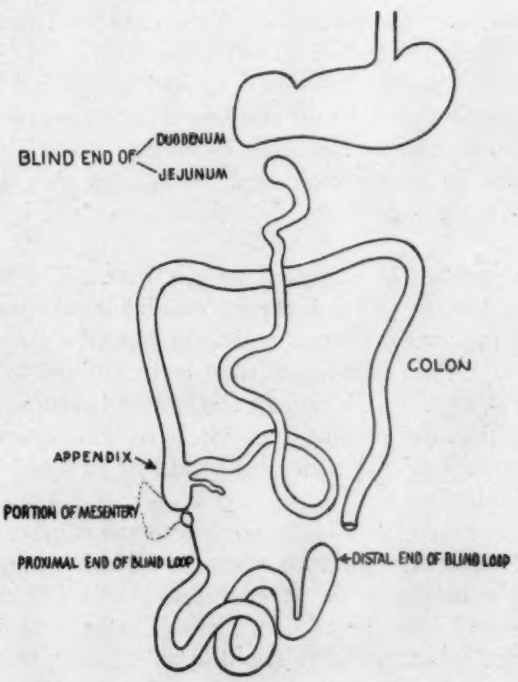

Fig. 2.—Diagrammatic sketch of the intestine.

Ileum: The mucosal lining had a typical appearance of small intestine with occasional goblet cells. The villi were fairly typical, as were also the crypts of Lieberkuhn. The lamina propria, submucosa, muscularis and serosa were not unusual.

Colon: The mucosa was somewhat irregular and torn. There were a lack of villi, an overabundance of goblet cells and many round glands typical of large intestine. The swollen pale epithelial cells were laden with mucinous pale blue material. Occasional scattered erythrocytes lay in the submucosa. A solitary lymphoid follicle was present.

Isolated Segment: The several sections taken of this were similar. A pink and pale blue amorphous material filled most of the lumen. The villous pattern was not as definite as usual, owing to some distention, but distinct villi were present. The comparatively few goblet cells were further suggestive of small

intestine. The mucinous lining cells were eosin staining and lacked the mucinous appearance of large intestine. There was no evidence of hypertrophy of the muscularis.

COMMENT

As has already been indicated, the case just described is one of duodenal atresia associated with an intestinal anomaly. In reviewing the literature it has been found that intestinal anomalies resembling the one in this case have been reported. In most instances the authors have had considerable difficulty in explaining the origin of the anomaly. Struthers,[1] for example, reported 2 cases of intramesenteric diverticulum of the ileum and ascribed the anomaly to vitelline duct rests. He took issue with Miller,[2] who ascribed an intramesenteric cyst to sequestration from the intestine. Similar anomalies reported by Abt and Strauss [3] and another recorded by Tisdall [4] were considered to be examples of Meckel's diverticulum in an unusual location. Evans and Keith,[5] in an analysis of cases of such anomalies, expressed the opinion that they probably originated from the embryonic diverticula described by Lewis and Thyng.[6]

A similar problem is presented in this case. The origin of the anomaly is not definite, although several possibilities are worthy of consideration. It may be an unusual variety of Meckel's diverticulum, but if so it is one which has been separated at both ends and this would certainly be difficult to prove. It may be an elongated cyst originating from a source other than the vitelline duct, viz. a supernumerary outgrowth, one of the aberrant epithelial nodes described by Lewis and Thyng [6] or a duplication of intestine.

The next consideration, and the one which seems most likely in this case, is that the isolated segment is a sequestration from the small intestine itself. The length of the anomalous segment (45 cm.) and the length of the small intestine (34 cm.) are together actually much less than the average length normally found in an 8 month old fetus, which is 249 cm.[7] It would seem logical to believe that the anomalous segment

1. Struthers, J. S.: Edinburgh M. J. **37**:403, 1930.

2. Miller, R. T.: Bull. Johns Hopkins Hosp. **24**:316, 1913.

3. Abt, I. A., and Strauss, A. A.: Meckel's Diverticulum as Cause of Intestinal Hemorrhage, J. A. M. A. **87**:991 (Sept. 25) 1926.

4. Tisdall, F. F.: Unusual Meckel's Diverticulum as Cause of Intestinal Hemorrhage, Am. J. Dis. Child. **36**:1218 (Dec.) 1928.

5. Evans, A., and Keith, A.: Brit. J. Surg. **17**:30, 1929.

6. Lewis, F. J., and Thyng, I. W.: Am. J. Anat. **7**:505, 1907-1908.

7. Scammon, R. E.: A Summary of the Anatomy of the Infant and Child, in Abt, I. A.: Pediatrics, Philadelphia, W. B. Saunders Company, 1923, vol. 1, p. 322.

is one of normal intestine which for some reason was cut off and left lying freely in the abdominal cavity. Although it is true that the histologic structure of the anomalous portion resembled the structure of small intestine, that fact cannot be taken as conclusive evidence that the segment is small intestine, since, as Poncher and Milles [8] have suggested, embryologic rests have such wide potentialities that the histologic appearance of the fully developed anomaly is of no aid in determining its origin.

SUMMARY

A case of duodenal atresia associated with an intestinal anomaly is presented. The intestinal anomaly is most likely a sequestration of the small intestine, although no conclusive evidence for such an origin exists.

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8. Poncher, H. G., and Milles, G.: Cysts and Diverticula of Intestinal Origin, Am. J. Dis. Child. **45**:1064 (May) 1933.

SEPTIC THROMBOPHLEBITIS OF THE CAVERNOUS SINUS IN A TWO YEAR OLD CHILD, WITH RECOVERY

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Septic thrombophlebitis of the cavernous sinus secondary to infection of the face or nose was formerly a uniformly fatal disease. In 1936 Grove [1] after surveying the literature concluded that the mortality was 100 per cent. Within the past two years there have been several recoveries following the use of sulfanilamide and its derivatives alone or in combination with heparin. Barnshaw,[2] Seydell [3] and Pace [4] each reported a cure following the use of sulfanilamide; Morrison and Schindler,[5] one following treatment with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), and C. T. and W. C. Wolfe,[6] one following the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). Schall [7] observed 3 cures obtained by the combined use of sulfathiazole and heparin. Erschler and Blaisdell,[8] who also used the combined method, reported a cure which was complicated by massive hematuria secondary to the treatment with heparin. The following report is of a recovery in a 2 year old child who was treated by heparin, sodium sulfathiazole given intravenously and Staphylococcus aureus antitoxin.

From the Surgical Service of Dr. Henry Roth and the Pediatric Service of Dr. Samuel Blauner, Lebanon Hospital.

1. Grove, W. E.: Septic and Aseptic Types of Thrombosis of the Cavernous Sinus, Arch. Otolaryng. **24**:29 (July) 1936.

2. Barnshaw, H. P.: Report of a Case of Bilateral Cavernous Sinus Thrombosis: Recovery Without Operative Intervention, J. M. Soc. New Jersey **36**:22 (Jan.) 1939.

3. Seydell, E. M.: Recovery from Thrombosis of the Cavernous Sinus, Arch. Otolaryng. **30**:429 (Sept.) 1931.

4. Pace, E.: Thrombosis of the Cavernous Sinus, Arch. Otolaryng. **33**:216 (Feb.) 1941.

5. Morrison, L. F., and Schindler, M.: Cavernous Sinus Thrombosis: Recovery Following Sulfapyridine Therapy, Arch. Otolaryng. **31**:948 (June) 1940.

6. Wolfe, C. T., and Wolfe, W. C.: Treatment of Thrombosis of Cavernous Sinus with Recovery, Arch. Otolaryng. **33**:81 (Jan.) 1941.

7. Schall, L. A.: Treatment of Septic Thrombophlebitis of the Cavernous Sinus, J. A. M. A. **117**:581 (Aug. 23) 1941.

8. Erschler, I. L., and Blaisdell, I. H.: Massive Hematuria Following Use of Heparin in Cavernous Sinus Thrombosis, J. A. M. A. **117**:927 (Sept. 13) 1941.

REPORT OF A CASE

E. C., a girl aged 2 years 3 months, was admitted to Lebanon Hospital Oct. 22, 1941 because of fever. She was a first-born child whose developmental history was normal. Two days prior to admission her temperature suddenly rose to 102 F. The next day it was 104 F., and although the cause of the fever was unknown sulfathiazole was prescribed by her family physician. The following morning, the day of admission to the hospital, she had a chill and several vomiting spells and the temperature rose to 106 F. It was learned subsequently that a small area of redness on the tip of the nose, noted at the time of admission, had been present for two days and that the child habitually stuffed bits of grass up into the nostrils.

Physical Examination.—The patient was a well developed girl weighing 30 pounds (13.5 Kg.), who appeared acutely ill. The right eye was closed because

Fig. 1.—The patient's appearance October 24, two days after admission.

of red, edematous swelling of the upper and lower lids, the edema and redness extending onto the right cheek. There was a small reddened area on the tip of the nose. In the right nasal vestibule was a small furuncle covered by dried exudate. Lifting of this crust yielded a drop of pus.

The pharynx and the tonsils were markedly congested. The right tympanic membrane was inflamed, but the landmarks were visible. The eyes were normal in appearance, there were no ocular palsies and the fundi were normal. The heart, lungs and abdomen were all normal. There were no abnormal neurologic findings.

The working diagnoses were (1) acute ethmoiditis secondary to an infection of the upper respiratory tract and (2) thrombophlebitis of the cavernous sinus secondary to the furuncle of the nose. The latter seemed the more likely diagnosis.

Laboratory Data.—The white cell count was 9,400 per cubic millimeter of blood, with 59 per cent polymorphonuclear cells, 17 per cent nonsegmented polymorphonuclear cells, 21 per cent lymphocytes and 3 per cent monocytes. The red blood cells numbered 4,100,000 per cubic millimeter, and the hemoglobin concentration was 70 per cent. Culture of the pus obtained from the furuncle in the right nostril yielded Staph. aureus, and culture of blood taken on the day of admission also yielded Staph. aureus. Subsequent cultures, of blood taken on the twenty-fourth and on the thirtieth of October, were likewise positive. Roentgen examination of both ethmoid regions showed slight cloudiness of the right ethmoid cells.

Course.—The child was given sulfathiazole orally, 60 grains (3.88 Gm.) per day, an initial dose of 30 grains (1.94 Gm.) and 15 grains (0.97 Gm.) four times

Fig. 2.—The patient's appearance October 27, five days after admission.

a day thereafter. Wet compresses of boric acid solution were applied to the tip of the nose, and drops of a 1 per cent aqueous solution of an ephedrine salt were instilled into the nostrils.

On October 23 the child's condition was worse; the temperature was 103 F. and the redness and swelling extended across the bridge of the nose, involving the left eyelids and the adjacent part of the left cheek and producing a butterfly effect resembling erysipelas. The redness, however, was neither as bright nor as delimited as in that condition.

On October 24 the bridge of the nose had become purplish but the tip remained unchanged. There were no ocular symptoms; nevertheless the diagnosis of septic thrombophlebitis of the cavernous sinus seemed definite. A transfusion of 200 cc. of citrated blood was given, and heparin in physiologic solution of sodium chloride containing 5 per cent dextrose was administered intravenously by the continuous drip method. The clotting time was measured hourly by the capillary tube

method. It was decided to prolong the coagulation time to a minimum of fifteen minutes, and 10 to 30 cc. of heparin per day was required to produce this effect. It was difficult to maintain the coagulation time at a uniform level. At times it would drop to below fifteen minutes, and occasionally it would rise to above an hour. Because of the wide and rapid fluctuations in the coagulation time, a Y tube arrangement for the intravenous therapy was used. One of the limbs was connected to a bottle containing the saline solution with 5 per cent dextrose and the other to a bottle containing the heparin in this solution. Each limb had its own clamp. When the coagulation time was longer than fifteen minutes the administration of the heparin solution was stopped and the use of the dextrose solution was started. By repeated testing day and night the coagulation time could be prevented from swinging too widely.

On October 25 the child was gravely ill. She was drowsy and listless. Both eyes were closed, and there was marked chemosis of the right eye. There were

Fig. 3.—The patient's appearance November 12, three weeks after admission.

no meningeal signs, and both eyes moved. The spleen was slightly enlarged. Treatment with Staph. aureus antitoxin, given intravenously, was started this day.

Dr. Joseph Ziporkes, ophthalmologist to Lebanon Hospital, examined the child and reported: "definite chemosis of the right eye; left disk normal; right disk pale; veins full and dilated."

On October 26, because of difficulty in raising the blood concentration of sulfathiazole by oral administration of the drug, a 5 per cent solution of sodium sulfathiazole was given intravenously, 15 grains four times a day. With continuation of this treatment it was possible to maintain a blood level of 8 mg. per hundred cubic centimeters. The tip of the nose assumed a bluish hue; it appeared gangrenous and a sanguinous purulent material exuded from a small perforation. This exudate yielded Staph. aureus on culture. The superficial veins of the bridge of the nose, the eyelids and the adjacent portion of the forehead were prominently dilated, and there were small necrotic areas in this region. The eye was proptosed and the chemosis increased.

On October 27 the child was brighter and seemed better although the local condition about the nose was worse. From then on improvement continued daily, but the proptosis persisted and receded only gradually. Intravenous therapy was discontinued at the end of two weeks, because repeated blood cultures were sterile and the temperature remained normal. Administration of sulfathiazole was continued by mouth for one week, although the temperature remained normal during this time.

The child received five transfusions of citrated blood in the first two weeks of her illness. Large doses of Staph. aureus antitoxin were given intravenously daily for ten days.

The hemoglobin concentration dropped to 49 per cent and the erythrocyte count to 2,740,000 during the second week; however, these values rose to 80 per cent and 4,100,000 by the sixteenth day of the patient's stay in the hospital and continued at a high level until the time of her discharge.

The local condition about the nose healed surprisingly well; only a small scar at the tip of the nose remained. The total period of hospitalization was one month, during the last seventeen days of which the temperature was normal.

COMMENT

The diagnosis of septic thrombophlebitis of the cavernous sinus in this case is based on: (1) the presence of a lesion in the nose which on culture yielded Staph. aureus; (2) repeated blood cultures showing that organism; (3) evidences of venous obstruction in the right retina, conjunctiva and eyelids, and visible and palpable phlebitis of the angular, frontal and supraorbital veins. The three additional diagnostic criteria suggested by Eagleton[9] in 1926 were not present. They are: (1) meningeal irritation; (2) paresis of the third, fourth and sixth nerves; (3) formation of abscesses in the neighboring soft tissues. While all the postulates have been present in some of the cases of recovery, in others not all have been present but the clinical history and observations warranted this diagnosis. This is true in our case, and it appears that no longer are all the criteria needed in any individual instance to justify the diagnosis of septic thrombophlebitis of the cavernous sinus. In fact, it seems that early treatment may prevent the development of the classic clinical picture. It arrests the process, thus preventing the complete thrombosis of the cavernous sinus, the meningitis, the soft tissue abscesses and the inflammatory involvement of the cranial nerves. The cardinal findings of a focus of infection together with definite invasion of the blood stream and signs of venous obstruction seem sufficient and should warrant immediate treatment with sulfathiazole and heparin.

The heparin is given for the prevention and treatment of the venous thrombosis. Undue prolongation of the coagulation time is apparently unnecessary and is not without its harmful effects. Attempts were made

9. Eagleton, W. P.: Cavernous Sinus Thrombophlebitis, New York, The Macmillan Company, 1926.

to keep the coagulation time in our patient at about fifteen minutes. It was difficult to do so because the fluctuations were sudden and occasionally wide, requiring constant supervision. This may have been due to the fact that the patient was a child who weighed only 30 pounds (13.5 Kg.).

The sulfathiazole was given over a long period to insure against relapses, which have occurred in cases previously reported. Because of the difficulty in maintaining a blood level above 6 mg. per hundred cubic centimeters by oral administration of sulfathiazole, sodium sulfathiazole had to be administered intravenously.

Rapid improvement after institution of treatment did not occur; at first the patient appeared worse and it was only after persistence with treatment that a favorable result became evident.

Staph. aureus antitoxin was administered intravenously in addition to the heparin and sodium sulfathiazole. It is difficult to appraise its value.

SUMMARY

Septic thrombophlebitis of the cavernous sinus occurred in a 2 year old child, and recovery was obtained. The diagnosis was based on the presence of a furuncle in the nose caused by Staph. aureus, invasion of the blood stream by the same organism, and evidences of venous obstruction of the right retina, conjunctiva and eyelids and phlebitis of the angular, frontal and supraorbital veins. Treatment consisted of repeated blood transfusions, oral administration of sulfathiazole and intravenous administration of heparin, sodium sulfathiazole and Staph. aureus antitoxin.

1882 Grand Concourse.

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Progress in Pediatrics

NUTRITIONAL EDEMA IN CHILDREN

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NUTRITIONAL DEFICIENCY AND NUTRITIONAL EDEMA

The terms nutritional deficiency and deficiency disease include an extremely wide field. Generally speaking, they are applied to conditions caused by deficiency of some of the materials essential for adequate nutrition, such as fat, carbohydrate, protein, vitamins and minerals. There are thirty-six known such essential constituents of the diet, and it is likely that there are others as yet unknown. It is easily conceivable that pure deficiency of one essential substance probably never exists except in experimental animals, while the ordinary clinical nutritional deficiency states are caused by a lack of several essential substances, with one or more of the clinical deficiency syndromes more apparent than the others. Moreover, the question is even more complicated than this, since little significant information has been obtained concerning the body's requirements for certain of these factors, and even less is known of the interrelation of many of these substances which undoubtedly exists in metabolism.

While nutritional deficiency diseases arise primarily from a dietary defect, they may be due secondarily to increased need, diminished absorption, increased destruction or diminished utilization of some essential or protective substance or substances, as a result of faulty dietary habits, food idiosyncracies, chronic alcoholic addiction or a diseased condition of the gastrointestinal tract, kidneys, heart or some other organ. That nutritional deficiency arises from excessive excretion of protein in cases of chronic nephrosis, from long-restricted diet in cases of gastric trouble and from impairment of absorption in cases of chronic colitis and dysentery is only too well known. Often the nutritional deficiency on the one hand and the disease condition of the patient on the other coexist, overlap and influence each other in one way or another.

Thesis submitted in partial fulfilment of the requirements for the degree of Master of Medical Science for work in pediatrics, Graduate School of Medicine, University of Pennsylvania.

The relation of nutritional deficiency to the occurrence of edema opens another interesting aspect. In 1817, Gaspard [1] described a dropsical condition occurring in inhabitants of France who lived for three months on potatoes, oat bread and other poor food and later only on plants and herbs during a famine. These people had edema of the extremities without ascites, icterus or an organic lesion in the liver or kidneys. The edema disappeared after they had received proper food. In 1915 Budzynski and Chelchowski [2] reported that a similar condition occurred among the people in Poland during a famine, when the principal foods were potatoes, soup and bread, with little fat and no milk or meat. Park [3] made a study of prisoners on war rations and concluded that the edema noted among them was due to underfeeding, especially of fats and proteins, and to ingestion of large amounts of fluid together with an increased amount of salt. Schiff [4] in his study of war edema found that edema occurred in subjects with long-standing chronic inanition who were fed a diet containing predominantly carbohydrates with little protein. Schittenhelm and Schlecht,[5] in their study in Germany, made observations similar to those of Park and in addition noted that edema was a late occurrence, preceded by a period of polyuria. They also noted a retention of chlorides, which were excreted as the edema subsided, and found by the refractometric method that values for serum proteins in 50 per cent of the cases were low, ranging from 4 to 6 per cent. Jansen,[6] using the Kjeldahl method, found serum proteins greatly reduced, and by comparison with the studies of hemoglobin advanced the conclusion that undernutrition caused a specific reduction of protein, due perhaps to failure of the process of regeneration of protein. Bruckman and Peters,[7] in 1930, in their study of serum protein with nutritional edema concluded that edema has been observed in patients with malnutrition only when the level of serum albumin is below normal. It almost invariably develops when the concentration of serum albumin falls below

1. Gaspard, B.: Effets des aliments herbacés sur l'économie animale, J. de physicl. exper. **1**:237, 1821; cited by Lusk, G.: The Physiological Effect of Undernutrition, Physiol. Rev. **1**: 523, 1921.

2. Budzynski, P., and Chelchowski, K.: Hunger Swelling in Poland, J. Trop. Med. & Hyg. **19**: 141, 1915.

3. Park, F. S.: War Edema, J. A. M. A. **70**:1826 (June 15) 1918.

4. Schiff, A.: Zur Pathologie der Oedemkrankheit, Vienna, 1917.

5. Schittenhelm, A., and Schlecht, H.: Ueber Oedemkrankheit mit hypotonischer Bradykardie, Berl. klin. Wchnschr. **55**:1138, 1918.

6. Jansen, W. H.: Die Oedemkrankheit, Deutsches Arch. f. klin. Med. **131**:144, 1919.

7. Bruckman, F. S., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: V. Serum Proteins and Malnutritional or Cachectic Edema, J. Clin. Investigation **8**:591, 1930.

3 per cent and is seldom found when the content exceeds 4 per cent. Nutritional edema, they feel, appears to be referable to a serum albumin deficiency brought about by wastage of body protein, the result of disease or of inadequate diet. Bruckman, D'Esopo and Peters [8] in their study of plasma protein in 57 patients with evidences of malnutrition showed that in these patients the total serum proteins were reduced, though in the reduction the albumin alone suffered. They also reported that temporarily high protein values were often found in patients with malnutrition during periods of hydration. In patients with infections globulin tended to be increased. For this reason they said, normal values for total proteins were found in certain patients with infectious diseases and malnutrition in spite of the presence of definite deficiency of serum albumin. Ling,[9] in 1931, studied 24 undernourished patients with edema, from a famine district in China, whose food for several months had consisted of corn meal, millet and salted turnip. He reported that the serum albumin values were all below the average normal level, while all the serum globulin values but 3 were within the normal range. After administration of a high protein diet edema soon disappeared, but the serum albumin required a considerable length of time to return to an average normal level. During the stage of undernutrition the basal metabolism was low and the protein metabolism showed a negative balance. When the nutrition was improved there were a positive nitrogen balance and high basal metabolism.

Kohman,[10] in her study of serum protein and experimental nutritional edema, found that edema developed in a large percentage of young rats fed a diet with carrot as the only source of protein. Salt did not seem to play an appreciable role in the production of edema, but ingestion of water decidedly led to earlier and more frequent development of edema. The edema, after appearance, could be successfully eliminated by supplying the diet with adequate protein. Frisch, Mendel and Peters [11] have confirmed Kohman's experiments and in addition have shown that serum protein deficiency regularly results from ingestion of diets containing inadequate amounts of protein.

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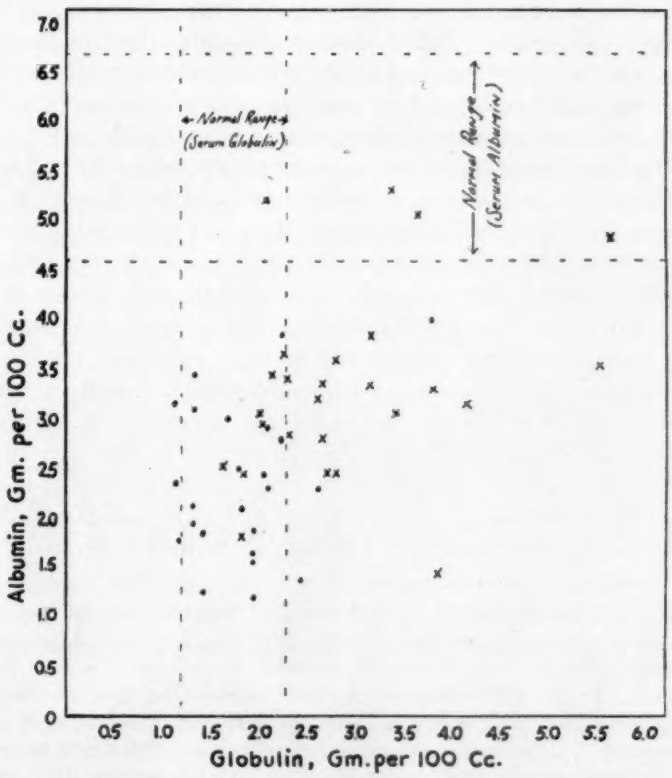
8. Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Proteins in Relation to Blood Hydration: IV. Malnutrition and Serum Proteins, J. Clin. Investigation **8**:577, 1930.

9. Ling, S. M.: Changes of Serum Proteins in Under-Nutrition, Chinese J. Physiol. **5**:1, 1931.

10. Kohman, E. A.: Experimental Production of Edema as Related to Protein Deficiency, Am. J. Physiol. **51**:378, 1920.

11. Frisch, R. A.; Mendel, L. B., and Peters, J. P.: The Production of Edema and Serum Protein Defiiciency in White Rats by Low Protein Diets, J. Biol. Chem. **84**:167, 1929.

The occurrence of edema in general, of which nutritional edema is one of the types, is concerned with the mechanism which controls the migration of fluid through the capillary walls as well as its transportation and distribution throughout the body and was hypothesized by Starling [12] in 1896 to be due to: (1) the hydrostatic pressure (blood pressure), which tends to drive fluid out of the blood vessels into the tissue, and (2) the osmotic pressure exerted by the proteins of the plasma, which



Serum protein values for patients with edema (dots) and for patients without edema (crosses).

tends to draw fluid into the blood. In 1917, Epstein [13] emphasized the role of hypoproteinemia in the development of nephrotic edema. Not until 1917 was the capillary wall thought to have exerted influence in the exchange of fluid between blood vessels and tissue spaces and con-

12. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1896.

13. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis; Methods for Its Alleviation, Am. J. M. Sc. **154**:638, 1917.

sequently in the development of edema.[14] Another factor in the development of tissue edema is the tissue pressure due to extravascular fluid distention and the nature of the tissue. This explains the fact that edema of the eyelids and of the ankles generally precede edema of other parts of the body. The part played by the amount of salt and fluid ingested by the patient is now generally thought to be only secondary.

Despite these factors in the development of edema in general, nutritional edema is generally attributed to the lowering of colloid osmotic pressure of the blood as a result of prolonged protein starvation. Several investigators (Govaerts,[15] Peters, Bulger, Eisenman and Wakeman,[16] Bruckman, Weach and Ling, and others) in different parts of the world have written on this aspect and reported that edema develops only when the value for serum albumin is below normal level, usually below 4 per cent. Actual nutritional edema was reproduced experimentally by Liu and his associates[17] in two persons suffering nutritional insufficiency in Peiping, China. By the use of "nitrogen-free" diets they produced or accentuated edema accompanied by changes in plasma proteins. A daily allowance of vegetable protein of approximately 1 Gm. per kilogram of body weight and 7 per cent of the total caloric intake was not sufficient to bring about distinctly positive nitrogen balance and increase in plasma protein and disappearance of edema. A higher amount of vegetable protein, namely 2 Gm. per kilogram and 14 per cent of the total caloric intake, was found necessary to overcome the edema. Animal protein in daily amounts of 1 Gm. per kilogram and 7 per cent of the total calories resulted in marked gain in nitrogen, increase in plasma proteins and disappearance of edema. The results compared favorably with those obtained when twice this amount of vegetable protein was fed.

Recently, Whipple and his collaborators[18] emphasized the metabolic importance of reserve materials available in the body for regeneration of

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14. Landis, E. M.: The Passage of Fluid Through the Capillary Wall, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 70.

15. Govaerts, P.: Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedèmas, Bull. Acad. roy. de méd. de Belgique **7**:356, 1927.

16. Peters, J. P.; Bulger, H. A., and Eisenman, A. J.: Total Acid-Base Equilibrium in Health and Disease, J. Clin. Investigation **3**:497 and 511, 1927. Peters, J. P.; Wakeman, A. M., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition, ibid. **3**:491, 1927.

17. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Nutritional Edema: Effects of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, Chinese J. Physiol. **6**:73, 1932.

18. Madden, S. C.; George, W. E.; Waraich, G. S., and Whipple, G. E.: Blood Plasma Protein as Influenced by Fasting, Infection and Diet Factors: Variable Reserve Stores of Plasma Protein Building Material in Dogs, J. Exper. Med. **67**:675, 1938.

plasma protein. Melnick, Cowgill and Burack [19] expressed the belief that plasmapheresis continued for two to six weeks and an adequate basal diet are essential to bring about a constant minimal production of plasma protein. An interesting finding was that under these conditions the addition of gelatin to the basal diet of a dog has little effect on the regeneration process but that gelation plus triptophane leads to a marked increase of plasma protein. Weech and Goettsch [20] found that beef serum was much more effective than beef muscle or casein in producing serum albumin regeneration.

It is believed that the edema which occurs in chronic wasting illnesses or as a symptom in certain dietary diseases is often associated with low protein in the blood, as in the case of inanition edema due to dietary restriction combined with tuberculous enteritis reported by Landis and Leopold,[21] in the 2 cases of fecal fistula of Wolferth [22] and in the cases of celiac disease of Marriott.[23]

Sometimes edema in association with keratomalacia is believed not to be due to lack of vitamin A. Weech [24] in his reported observation of 13 cases of keratomalacia included 5 cases of edema. He stated that in China keratomalacia is usually not associated with edema; not infrequently, however, the combination is found. In his opinion the edema is a separate disorder, exhibited by patients with keratomalacia not as a manifestation of vitamin A deficiency but as the expression of an associated nutritional disorder. Harden and Zilva [25] observed that in spite of the administration of enough yeast to furnish an adequate amount of the vitamin B complex edema developed in a monkey which was kept

19. Melnick, D.; Cowgill, G. R., and Burack, E.: The Influence of Diet upon the Regeneration of Serum Protein: I. Standardization of Experimental Technique, J. Exper. Med. **64**:877, 1936. Melnick, D., and Cowgill, G. R.: The Influence of Prolonged, Intensive Plasmapheresis upon the Ability of the Organism to Regenerate Serum Protein, ibid. **66**:493, 1937.

20. Weech, A. A., and Goettsch, E.: Dietary Protein and the Regeneration of Serum Albumin: I. Method of Assay and Discussion of Principles, Bull. Johns Hopkins Hosp. **63**:154, 1938; II. Comparison of the Potency Values of Beef Serum, Beef Muscle and Casein, ibid. **63**:181, 1938.

21. Landis, E. M., and Leopold, S. S.: Inanition Edema Associated with Tuberculous Enteritis, J. A. M. A. **94**:1378 (May 3) 1930.

22. Wolferth, C. C.: Inanition Edema Associated with Alimentary Disturbances in Adults, M. Clin. North America **8**:785, 1924.

23. Marriott, W. M.: Infant Nutrition, St. Louis, C. V. Mosby Company, 1930.

24. Weech, A. A.: Association of Keratomalacia with Other Deficiency Diseases, Am. J. Dis. Child. **39**:1153 (June) 1930.

25. Harden, A., and Zilva, S. S.: Oedema Observed in a Monkey Fed on a Diet Free from the Fat-Soluble "A" Accessory Food Factor and Low in Fat, Lancet **2**:780, 1919.

on a diet of 250 to 300 Gm. of polished rice daily. This would suggest that the chronic edema in many cases of beriberi is not due to vitamin B deficiency. Weech and Ling [26] observed a case of an edematous type of scurvy in which there was a reduction of the serum protein.

Plasma protein formation may be stimulated by the intravenous injection of a complete mixture of amino acids, according to Elman.[27] Dogs depleted of plasma protein by hemorrhage and fasting showed a response within twenty-four hours following such treatment.

DIETARY CONDITIONS OF REFUGEES AND POORER CLASSES IN SHANGHAI

An excellent opportunity has always existed in China, even during peace times, for observing patients suffering from malnutrition primarily of dietary origin, sometimes accompanied with edema. This is accounted for by the restricted diet of the peasants and laboring classes, due to their poor financial condition, their lack of understanding regarding health, and the lack of proper health supervision on the part of the government. Dietaries published by H. Wu and D. Y. Wu [28] before the present war have shown that the bulk of protein and energy-producing material in the diet of these people in China is mainly of vegetable origin, being furnished chiefly by cereals, such as wheat, rice, corn and millet. Such a diet contains less than the optimum amount of protein and relatively small amounts of fat, calcium and phosphorus and often is deficient in vitamins A and D and the B complex.

The dietary standards of the peasants and laboring classes and even of many of the middle class people have become much worse since the onset of the present Sino-Japanese war, in 1937. In the war zones most of the homes have been devastated, destroyed or ransacked and the people have had to live in such miserable conditions as are neither describable nor imaginable. There is no such thing as hygiene or proper diet. They eat whatever they can get hold of, and there is very little to be had. Those that are fortunate enough to get out of the war zones to places of greater safety, such as the foreign settlements, either are sent to refugee camps, hurriedly installed by philanthropic organizations, the Red Cross or relief institutions, or have to struggle on in a society where

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26. Weech, A. A., and Ling, S. M.: Nutritional Edema: Observations on the Relation of Serum Proteins to the Occurrence of Edema and to the Effect of Certain Inorganic Salts, J. Clin. Investigation **10**:869, 1931.

27. Elman, R.: Intravenous Injection of Amino Acids in Regeneration of Serum Protein Following Severe Experimental Hemorrhage, Proc. Soc. Exper. Biol. & Med. **36**:867, 1937.

28. Wu, H., and Wu, D. Y.: Study of Dietaries in Peking, Chinese J. Physiol. (Rep. Ser.), 1928, no. 1, p. 135.

the cost of living is more than they can afford and so live under conditions even worse than those of the refugee camps. It is from observations of these unfortunates, mostly from the different refugee camps, that the data for this thesis were obtained. Investigation of the actual dietary conditions of these poor war refugees of Shanghai has not turned out to be as difficult a problem as was expected. While there are a few extremely well managed and well provided camps, sponsored usually by individuals, serving a properly mixed and balanced diet with animal protein a few times each week, they constitute such a negligible percentage that they are not included in this report. The diets of most of the camps are essentially similar in quality and quantity. They are extremely monotonous throughout the year and deficient in protein (especially of the animal type), fat, calcium, phosphorus, iron and vitamins, especially the B complex, C, A and D. Supplementary amounts of the last two vitamins are supplied in a few camps by giving pure cod liver oil to the refugees, but this is often refused because of the taste. The following representative diet is a result of a careful study of the dietary conditions of fifteen large camps, either for children only or for children and adults and widely located throughout the city of Shanghai.

GENERAL DIET OF REFUGEE CAMPS

Children 1 to 2 Years of Age

These refugees are fed on congee[29] supplemented with soybean milk (about 1 pint [475 cc.] daily).

Mother's milk may be given irregularly if available.

Cod liver oil is given once or twice daily in a few camps (but often neglected).

Children 2 to 6 Years of Age

7 a. m.: A bowl of congee with some salted parsnip.
10 a. m.: Half a pint (240 cc.) of soybean milk.
12 noon: A bowl of boiled rice with some salted turnips.
4 p. m.: Half a pint (240 cc.) of soybean milk.
6 p. m.: A bowl of boiled rice with some salted turnips.

Fresh vegetables may be given once or twice weekly at meals, and vegetable soup may be given in some camps once weekly instead of soybean milk. In some camps cod liver oil is given once or twice daily.

Red gram beans and cracked wheat are sometimes added to the boiled rice in some camps.

In a very few camps, a dish of meat or fish is given twice a month for older children.

Children 6 to 12 Years of Age

The diet is essentially the same as that for the children 2 to 6 years of age, except that bean cake is given once daily instead of soybean milk.

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29. Congee is prepared by adding 150 Gm. of washed white rice to 500 cc. of water and boiling for two hours.

NUTRITIVE VALUE OF FOODS USED

The nutritive values of the different foods used in the refugee camps are given for reference.

Kind of Food	Amount Per Gram			
	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
Red gram beans	0.207	0.005	0.584	3.21
Turnips	0.006		0.056	0.25
Salted turnip top	0.026	0.001	0.041	0.28
Soybean, yellow	0.392	0.174	0.254	4.15
Rice	0.096	0.002	0.796	3.59
Wheat flour	0.112	0.010	0.749	3.53
Soybean milk (1 pint)	14.800	4.800	8.000	136.00

The vitamin contents of these foods are as follows:

Kind of Food	Vitamin A	Vitamin B	Vitamin C
Red gram beans			
Soy beans	+	++++	—
Turnips	?	++	++
Rice, polished	—	—	—
Soybean milk	+++	++	—
Wheat flour, white	—	?	—

The mineral contents of these foods (in milligrams per hundred grams) are as follows:

Kind of Food	Calcium	Phosphorus	Iron
Red gram beans	96	290	4.4
Turnips	45	18	0.9
Rice, polished	18	130	1.2
Soybean milk	25	45	2.5
Wheat flour, good	20	92	1.0
Wheat flour, poor	39	360	3.7

MATERIAL FOR STUDY

The data for this thesis were collected from study of the inpatients admitted to the medical pediatrics department of the American Hospital for Refugees, Shanghai, China, of which I am personally in charge. The hospital is maintained for the sick refugees of the present war in this region. A large proportion of the patients treated in this hospital come from the different refugee camps, the diets of some of which have been briefly analyzed and discussed. The rest of the patients are poor laborers, coolies, beggars and unemployed people, who are often in even a worse condition physically and on a poorer diet than the camp refugees. As it is the purpose of this hospital to admit only extremely sick patients who cannot be treated otherwise and most of the time there are more applicants than the hospital can admit, naturally patients with uncomplicated nutritional edema in the early stages cannot be hospitalized. All the persons considered in this research, therefore, had other serious diseases associated with or complicating the edema or had edema so severe that it could not possibly be dealt with outside of the hospital. This is also true of the nonedematous patients studied, and it is one of

the principle reasons for the high mortality in the medical pediatrics department, as will be partly shown later in this report. None of the ambulatory patients treated in the outpatient department were included in this study, for they were usually hard to manage and to follow up for research purposes; nor were any included who came for surgical ailments or for complaints such as ophthalmologic, otolaryngologic, urologic or dermatologic ones, which were outside of the control of my associates and me. All the patients in this study were under 12 years of age. The clinical tests were done by the clinical laboratory of the hospital, while the special protein determinations (biuret method used in all cases) were done by the biochemical laboratory of the Pennsylvania Medical School, St. John's University, under the directorship of Mr. R. J. Salmon, and the necropsies were done by Dr. C. L. Dale, of the pathology department of the same school.

DATA

This study covers a period of one year and ten months (from December 1937 to October 1939). Although there were 903 patients admitted for various diseases to the medical pediatrics department, among whom 433 patients, or 47.95 per cent of the total, had apparent clinical manifestations of nutritional deficiency of various kinds, 292 children, or 67.44 per cent of those suffering from nutritional deficiency and 32.33 per cent of the total number admitted, did not have clinical edema that could be detected by the ordinary physical examination of any part of the body, while 141 children had clinically apparent edema of varying degrees in different parts of the body. Of the 141 edematous children, there were 7 with acute hemorrhagic nephritis, 1 with chronic parenchymatous nephritis and 3 with cardiac disease. These 7 patients were excluded from this study, for it was thought that the edema might be the result, at least partly, of cardiac or nephritic lesions. Thus there were 130 patients (30.02 per cent of those suffering from nutritional deficiency and 14.40 per cent of the total number admitted) with edema that was considered to be of nutritional origin.

Generally speaking, regardless of the presence or absence of tissue edema, all these patients with nutritional deficiency showed wasting of tissue that could be attributed only to undernourishment in varying degrees. Instead of being rosy and vitally colored, their skin was pale and yellowish. There were apparent disappearance of fatty cushions and wasting of muscles of the head, body and extremities. They generally looked much older than they really were, and some of them were decidedly senile looking, with wrinkles over the face and body and marked predominance of nasolabial folds (this was usually more apparent among those without edema). Their lips were bright cherry red, dry or slightly cyanotic and many were covered with excoriations. Their hair was generally scanty, dry and brittle, and glossitis and stomatitis often were present in varying degrees. Another interesting feature that was generally present in these cases was a peculiar involvement of the teeth,

consisting of brownish discoloration and decay, more or less eating up the teeth, affecting particularly the upper incisors. Sometimes half of the teeth or even the whole structure up to the roots was eaten away. Psychologically, instead of being friendly or of pleasing disposition, they were usually fretful and unfriendly, crying a great deal. Development was markedly impeded, both physically and mentally.

The cutaneous changes in these children did not seem to be affected noticeably by the presence of edema. They consisted mainly in roughening and coarsening of the usually fine or delicate texture of infantile or childish skin. Keratotic changes of the cutaneous epithelium were common. They appeared as a group of dark gray coarse papular lesions of varying sizes, usually surrounded by a zone of grayish or brownish pigmentation seen over the chest, the shoulders, the abdominal wall, the posterior and anterolateral aspects of the thighs, the extensor surfaces of the forearms and the backs of the hands. It is a highly debatable question whether the underlying cause for this condition is a deficiency of vitamin A or of the B complex. However, the cutaneous lesions and the clinical picture differed from those of vitamin B deficiency or pellagra seen in this part of the world; and the cutaneous lesions generally responded favorably to treatment with cod liver oil and even more noticeably to administration of vitamin A in concentrated form. It would not be surprising if the condition were to be demonstrated later to be the result of a multiple deficiency in which both vitamin A and the B complex play a great part.

The most noticeable evidence of vitamin deficiency in these children was the often present ocular lesions of xerophthalmia and keratomalacia, both believed to be due to deficiency of vitamin A. No difference was recorded in the ocular symptoms and pathologic changes between the patients with and those without edema. They presented a diffuse dryness or xerosis of the bulbar and palpebral conjunctiva and sometimes a typical Bitot spot (a triangular dry spot in the canthus with the base inward toward the corneal limbus), usually accompanied with blepharospasm and photophobia. Lacrimation was sometimes profuse and sometimes lacking. The bulbar conjunctiva frequently took on a light grayish brown pigmentation, which might be pronounced around the limbus in the form of a thin brownish ring. Infection of the conjunctiva, either bulbar or palpebral, xerosis and fine haziness over the cornea, iritis, and softening of the cornea (keratomalacia) were present in some of the patients. Treatment with vitamin A usually resulted in prompt and definite improvement.

No clinical difference was noticed between beriberi or vitamin B_1 (thiamine) deficiency in patients with edema and in those without it, except with the "wet type" of beriberi, due to cardiac involvement,

patients with which were excluded from the series with edema. The children had anorexia, palpitation and slight arrhythmia of the heart, absence of knee jerks and tenderness of the calf muscles; some of the older children had numbness of the legs. As seen, the condition did not differ in any way from the usual peripheral neuritis variety of vitamin B_1 (thiamine) deficiency.

Genuine clinical scurvy or other vitamin C deficiency was rare among our patients. Glossitis, swollen gums, pyorrhea, stomatitis and gingivitis, however, were often seen. Vincent's angina and noma sometimes appeared as complications both among edematous and among nonedematous patients; they did not differ in clinical manifestations in the two groups. Whether the oral inflammation and infection were the result of vitamin C deficiency is a moot question. Attempts have been made to estimate the ascorbic acid content of the urine and blood of the children with these conditions, but the results of the tests are far from furnishing conclusive evidence of vitamin C deficiency.

The presence of edema does not seem to affect the type of clinical manifestations of rickets or other vitamin D deficiency. Hypotonicity of the musculature, and chronic inflammation of the mucosa of the gastrointestinal and respiratory tracts leading to chronic indigestion and infection of the respiratory tract were noticed in both edematous and nonedematous children. The usual changes of the cranium (prominent bosses over the forehead and frontal, temporal or parietal region, asymmetry of the head and delayed closure of the fontanels and cranial sutures), the rachitic rosary, the deformity of the thoracic cage (sinking of the upper part of the chest with flaring of the lower ribs, those covering the liver and the upper portion of the abdomen) and the changes of the long bones (we encountered more bow legs than knock knees) were found in both edematous and nonedematous patients.

The presence or the absence of edema did not noticeably modify the clinical symptoms and signs of associated or complicated diseases; infections of the skin, such as impetigo and pyoderma; noma; otitis media; infections of the respiratory tract, such as bronchitis, pulmonary tuberculosis and bronchial and lobar pneumonia; gastrointestinal diseases, such as dysentery, typhoid and enterocolitis; urologic infections, such as pyelitis; parasitic diseases, such as ascariasis, ancylostomiasis, amebiasis, scabies, schistosomiasis (japonicum), infection with Fasciolopsis buski and malaria.

The age distribution of the children with nutritional edema is shown in table 1. Sixty-nine, or 53 per cent, of the patients with this condition were in the first six years of life, while 61, or 46.93 per cent, were in the next six years of life.

For comparison, the age distribution of the 292 patients with nutritional deficiency without edema are also presented (table 2). It is noted that 232 of these patients, or 79.45 per cent, were in the first six years of life, while 60, or 20.55 per cent, were in the 6 to 12 year group. It is noted also that 126, or 43.15 per cent, of the nonedematous children were under 2 years of age, while among the edematous children only 12, or 9.23 per cent, were below the 2 year limit.

As a whole, nutritional deficiency, whether accompanied with edema or not, occurred with practically the same frequency in the two sexes. Among the patients with edema there were 63 boys and 67 girls, while among those without edema there were 147 boys and 145 girls. Even in

TABLE 1.—*Age Distribution of Children with Malnutrition with Edema*

Age in Years	No. of Patients	Sex		Per Cent
		M	F	
0-2	12	2	10	9.23
2-6	57	29	28	43.84
6-12	61	32	29	46.93
Total	130	63	67	100.00

TABLE 2.—*Age Distribution of Children with Malnutrition Without Edema*

Age in Years	No. of Patients	Sex		Per Cent
		M	F	
0-2	126	69	57	43.15
2-6	106	50	56	36.30
6-12	60	28	32	20.55
Total	292	147	145	100.00

the different age groups the distribution was comparable (tables 1 and 2), except that in the 0 to 2 year group of patients with edema there were only 2 boys and 10 girls while in the similar age group of the nonedematous patients there were 69 boys and 57 girls.

The preexisting diseases of the children with nutritional edema that may have been contributing factors in the final development of the tissue edema were rather difficult to determine, as most of the children were brought in by very ignorant parents and many were even without parents. Thus for 104 patients the existence of preexisting diseases could not be determined. Nine children had had measles before the edema was noticed by the patient or his parents, 3 had had smallpox, 3 had had lobar pneumonia, 3 had had typhoid and 1 each had had cholera, pertussis, bronchiectasis and malaria (table 3).

As previously mentioned, the hospital admits only patients with the more serious diseases; hence in practically all the patients with nutritional deficiency who were treated the condition was associated with

other illness. Only 3 patients (2.30 per cent) in the edematous group and 8 (2.74 per cent) in the nonedematous group had uncomplicated pure nutritional deficiency.

TABLE 3.—*Preexisting Diseases of Patients with Malnutrition with Edema*

Disease	No. of Patients	Per Cent
Enterocolitis	4	3.07
Measles	9	6.93
Smallpox	3	2.31
Cholera	1	.77
Pertussis	1	.77
Bronchiectasis	1	.77
Lobar pneumonia	3	2.31
Malaria	1	.77
Typhoid	3	2.30
No preexisting disease known	104	80.00

TABLE 4.—*Associated Diseases of Patients with Malnutrition*

	Malnutrition With Edema		Malnutrition Without Edema	
Associated Diseases	No. of Patients	Per Cent	No. of Patients	Per Cent
Ascariasis	32	24.61	71	24.31
Ancylostomiasis	5	3.84	11	3.76
Schistosomiasis	1	.77	1	.34
Kala-azar	2	1.54	.....	.....
Infection with clonorchis sinensis	1	.77	.....	.....
Malaria	8	6.15	16	5.49
Infection with fasciolopsis buski	2	1.54	4	1.37
Pyelitis	6	4.61	1	.34
Lobar pneumonia	7	5.38	7	2.39
Tuberculosis	22	16.92	29	9.93
Bronchopneumonia	17	13.07	100	34.24
Bronchiectasis with pulmonary abscess	1	.77	.....	.....
Empyema	3	2.30	.....	.....
Amebic dysentery	3	2.30	1	.34
Enterocolitis	45	34.61	83	28.42
Beriberi	32	24.61	46	15.75
Rickets	50	38.46	173	59.24
Xerophthalmia	23	17.70	42	14.38
Otitis media	30	23.07	47	16.09
Noma	11	8.46	11	3.76
Typhoid	1	.77	15	5.13
Osteomyelitis	1	.77	.....	.....
Pyoderma	5	3.84	12	4.10
Retropharyngeal abscess	1	.77	.....	.....
Gonococcic vaginitis	1	.77	.....	.....
Meningococcic meningitis	....	.....	.....	.....
Influenzal meningitis	....	.....	.....	.....
Anaemia infantum (pseudoleukemia)	1	.77	.....	.....
No associated disease	3	2.30	8	2.74

For comparison between the edematous group and the nonedematous group, the diseases associated with nutritional deficiency and their age incidence are listed in table 4.

It is noted that enterocolitis and xerophthalmia had a slightly higher incidence in the edematous than in the nonedematous group. Beriberi,

otitis media, tuberculosis, noma and lobar pneumonia were appreciably more frequent in the group with edema. However, rickets, bronchopneumonia and typhoid were more frequent in the nonedematous group. The parasitic diseases, such as ascariasis, ancylostomiasis, schistosomiasis, fasciolopsis infection and malaria, occurred with about the same frequency in the two groups.

There were a few complications (or rather diseases that developed while the patients were in the hospital) which occurred among the patients with nutritional edema, but they did not present any feature that needs special comment. They are listed in table 5.

Determinations of serum protein (total protein, albumin and globulin) were done for 26 patients with nutritional deficiency accompanied with edema, chosen at random (table 6); for 16 of these the tests were repeated after a varying period of treatment in the hospital. Such determinations were made also for 26 patients with nutritional deficiency without edema, also chosen at random (table 7). The biuret technic [30] was used in all the determinations.

TABLE 5.—*Complications Occurring in Edematous Patients with Malnutrition*

Disease	No. of Cases	Per Cent
Smallpox	1	.77
Bronchopneumonia	4	3.07
Diphtheria	2	1.54
Measles	2	1.54
Mastoiditis	1	.77
Tuberculous peritonitis	1	.77
Malaria	1	.77
Nephritis	2	1.54
Otitis media	1	.77
No complication	115	88.46
	130	

Among the 26 patients with edema whose serum protein was studied, in the initial determinations 92.31 per cent (all except 2) had values for total protein below the low limit of normal (normal range, 6.5 to 8.2 per cent). The exceptional patients were:

1. A child with nutritional edema with beriberi and typhoid, who had total serum protein 6.84 per cent, albumin 3.55 per cent, globulin 3.29 per cent, and albumin-globulin ratio 1.08. The degree of edema was slight. In this child's case the test was done during the convalescent stage, when edema had almost subsided.

2. A child with nutritional edema associated with bacillary dysentery, who had total serum protein 7.8 per cent, albumin 4.03 per cent, globulin

30. Fine, J.: Biuret Method of Estimating Albumin and Globulin in Serum and Urine, Biochem. J. **29**:799, 1935.

TABLE 6.—*Values for Serum Protein and Other Data on Blood of 26 Patients With Malnutrition With Edema*

Case No.	Diagnosis	Sex	Age	Serum Protein, % Total	Alb.	Glob.	A/G Ratio	R.B.C.	Hgb.	Color Index	Result	Degree of Edema
1.	Bacillary dysentery	M	4	3.03	1.80	1.23	1.46	2,400,000	52	1.1	Death	+
2.	Beriberi	F	12	3.21	1.23	1.98	0.67	2,070,000	30	0.75	Improved	+++
				5.00	2.30	2.70	0.84					
3.	Tuberculous peritonitis	F	11	3.36	1.89	1.47	1.30	3,250,000	65	1.0	Death	+++
				4.80	2.82	1.89	1.42					
4.	Bronchopneumonia	F	2	3.45	2.12	1.33	1.59	3,850,000	56	0.7	Death	++
5.	Cancrum oris; bronchopneumonia	M	7	3.54	1.56	1.98	0.76	3,920,000	65	0.8	Death	++
6.	Malaria	F	4	3.54	2.39	1.15	2.01	4,090,000	84	0.9	Relieved	+
				6.64	4.18	2.46	1.80					
7.	Rickets; xerophthalmia	M	1½	3.66	1.68	1.98	0.84	5,820,000	85	0.7	Improved	+++
				5.52	2.74	2.78	0.80					
8.	Bronchopneumonia	F	7	3.84	1.87	1.97	0.50	5,230,000	77	0.7	Improved	+
				6.30	3.36	2.94	1.10					
9.	Pyoderma; otitis media	F	2½	4.02	2.16	1.86	1.16	3,700,000	70	0.9	Improved	+
				7.93	4.44	3.49	1.29					
10.	Rickets; cervical adenitis	F	1¾	4.26	1.94	1.32	1.47	3,050,000	54	0.9	Improved	+
				4.04	2.17	1.87	1.16					
11.	Bacillary dysentery; bronchopneumonia; xerophthalmia	F	3	4.30	3.17	1.13	2.80	4,980,000	90	0.9	Death	++
12.	Malaria, subtertian	M	3	4.32	2.51	1.81	1.38	1,380,000	22	0.8	Death	++
13.	Bronchopneumonia; bacillary dysentery	F	10	3.84	1.38	2.46	0.74	4,440,000	86	1.0	Death	+++
14.	Bacillary dysentery; pulmonary tuberculosis	F	6	4.44	2.30	2.10	1.09	2,830,000	45	0.8	Improved	++
				6.21	3.91	2.30	1.70					
15.	Ascariasis; rickets; bronchopneumonia	F	1½	4.47	3.12	1.35	2.50	2,720,000	44	0.8	Improved	++
				5.70	3.55	2.15	1.65					
16.	Beriberi; hilar tuberculosis	M	7	4.50	2.47	2.03	1.22	3,330,000	71	1.1	Relieved	++
17.	Pyoderma; bronchopneumonia	F	11	4.68	3.00	1.68	1.78	2,950,000	36	0.6	Death	++
18.	Xerophthalmia; chronic enteritis	M	6	4.89	2.28	2.61	0.87	2,310,000	40	0.9	Relieved	++
				6.66	3.48	3.18	1.09					
19.	Malaria, benign tertian; rickets	F	3	4.95	.....	.....	.....	4,520,000	75	0.8	Improved	++
20.	Ulcerative stomatis; hilar tuberculosis	M	2	5.07	2.80	2.26	1.23	2,950,000	57	1.0	Improved	+
				7.50	4.22	3.28	1.29					
21.	Beriberi; hilar tuberculosis	M	9	5.08	2.92	2.10	1.35	4,170,000	72	0.9	Relieved	++
				5.52	3.58	1.94	1.84					
22.	Xerophthalmia; bacillary dysentery	F	4	2.70	1.25	1.45	0.86	4,890,000	96	1.0	Improved	++
				5.64	2.47	3.17	0.78					
23.	Beriberi; impetigo	M	7	6.12	3.84	2.28	1.66	3,260,000	76	1.2	Relieved	++
				7.26	4.32	2.94	1.40					
24.	Hilar tuberculosis; rickets; diphtheria	F	2 10/12	4.76	3.44	1.32	2.60	6,650,000	67	0.5	Transferred	+
				6.52	2.87	3.65	0.70					
25.	Beriberi; typhoid *	M	4	6.84	3.55	3.29	1.08	4,330,000	76	0.9	Relieved	+
26.	Bacillary dysentery	F	1½	7.80	4.03	3.77	1.08	4,330,000	82	0.9	Improved	++
				5.58	4.27	1.31	3.20					

* The serum protein determination was done when edema was subsiding.

TABLE 7.—*Values for Serum Protein and Other Data on Blood of 26 Patients With Malnutrition Without Edema*

Case No.	Diagnosis	Sex	Age	Serum Protein, %			A/G Ratio	R.B.C.	Hgb.	Color Index	Result
				Total	Alb.	Glob.					
1.	Malnutrition; keratomalacia	F	4	3.66	1.82	1.84	0.96	6,060,000	122	1.0	Improved
2.	Bacillary dysentery; xerophthalmia	M	2	4.23	2.57	1.66	1.54	5,370,000	85	0.9	Improved
3.	Tuberculosis and cavity following measles (terminal edema)	M	2½	4.32	2.47	1.86	1.30	5,950,000	59	0.5	Death
4.	Typhoid (6 days outside)	M	10	4.52	2.81	2.71	1.65				Relieved
5.	Bacillary dysentery (Hiss-Russell)	M	10	4.98	2.95	2.03	1.45	3,443,000	83	1.2	Death
6.	Bronchitis; otitis media; ascariasis	F	2½	5.04	3.05	1.99	1.55	2,660,000	66	1.3	
7.	Acute bronchitis; enteritis; pyelitis; malignant malaria O. M.	F	2	5.19	2.45	2.74	0.9		55	0.9	Improved
8.	Typhoid	F	9	5.10	2.45	2.74	0.9	4,280,000	72	0.9	Still here
9.	Hilar tuberculosis	F	8	5.22	2.86	2.36	1.21	2,760,000	55	0.6	Hilar tuberculosis improved
10.	Typhoid; gangrenous ulceration in groin; hilar tuberculosis	F	5	5.38	1.45	3.88	0.37	3,930,000	50	0.6	Hilar tuberculosis improved
11.	Acute bronchitis	M	2 2/12	5.61	3.46	2.15	1.60	3,630,000	75	1.0	Improved
12.	Acute bronchitis	M	1½	5.70	3.40	2.30	1.40	4,450,000	70	0.8	Relieved
13.	Bronchitis; acute otitis media; severe rickets	M	1 10/12	5.73	3.19	2.59	1.25	4,040,000	65	0.8	Improved
14.	Tuberculosis	M	12	5.94	3.65	2.29	1.59	3,340,000	62	0.9	Still here
15.	Typhoid	M	12	6.18	3.40	2.70	1.20	4,910,000	86	0.9	Relieved
16.	Typhoid	M	12	6.50	3.07	3.43	0.89	.....	.....	.....	Relieved
17.	Typhoid	F	9	6.50	3.62	2.85	1.27	2,520,000	78	1.0	Relieved
18.	Rickets; beriberi; malaria	M	4	6.51	3.34	3.17	1.08	5,680,000	63	0.6	Improved
19.	Bronchopneumonia	F	2	7.02	3.85	3.17	1.24	4,510,000	75	0.8	Death
20.	Fasciolopsiasis; tuberculous adenitis	F	6	7.14	3.28	3.86	0.85	6,390,000	87	0.7	Improved
21.	Tuberculosis	F	6	7.29	3.16	4.18	0.74	4,130,000	55	0.7	Still here
22.	Hilar tuberculosis	M	8	7.35	5.23	2.12	2.77				Death
23.	Malnutrition; tuberculosis; otitis media	M	4	8.70	5.30	3.40	1.56	5,230,000	80	0.8	Improved
24.	Lobar pneumonia, type XVI	M	10/12	8.72	5.05	3.67	1.38	3,810,000	65	0.8	Relieved
25.	Tuberculosis; otitis media	F	12	9.06	3.52	5.53	0.64		65		Still here
26.	Bacillary dysentery	M	1¼	10.57	4.86	5.71	0.68				Improved

3.77 per cent and albumin-globulin ratio 1.08. The degree of edema was moderate.

In the determinations of serum albumin, the initial values for all the 26 patients with edema were found to be below the normal level (4.5 per cent). The values for 19 of the children, 76 per cent, were below the critical level for edema, of 3 per cent; 10 children had values between 2 and 3 per cent and 9 between 1 and 2 per cent. There were only 6 children, or 24 per cent, whose serum albumin values were between 3 and 4.5 per cent. Of these, only 1 had a concentration a little over 4 per cent; this was a child with bacillary dysentery associated with moderate edema, with total serum protein 7.8 per cent, albumin 4.03 per cent, globulin 3.77 per cent and albumin-globulin ratio 1.08.

In the determinations of serum globulin, in the group with edema 19 patients, or 86.93 per cent, had values within the normal range (1.2 to 2.3 per cent). There were 2 whose values were below the lower normal limit. One was a child with nutritional edema and malaria, with total serum protein 3.54 per cent, albumin 2.39 per cent, globulin 1.15 per cent and albumin-globulin ratio 2.01; after ten days of hospital diet and treatment, the total serum protein rose to 6.64 per cent, the albumin to 4.18 per cent, the globulin to 2.48 per cent and the albumin-globulin ratio to 1.8. Another was a child with nutritional edema associated with bacillary dysentery, bronchopneumonia and xerophthalmia, with total serum protein 4.30 per cent, albumin 3.17 per cent, globulin 1.13 per cent and albumin-globulin ratio 2.8. Four of the patients, or 15.38 per cent, had serum globulin values above the high limit of normal. Two of these had associated bacillary dysentery; 1 had xerophthalmia and chronic enteritis, and 1 had beriberi and typhoid.

In these determinations for the patients with nutritional edema, the type of associated disease did not show any specific effect on the level of total serum protein, albumin or globulin or on the albumin-globulin ratio.

Repetition of the serum protein determinations was done for 16 patients after one week to two months of treatment in the hospital. Definite improvement, in some instances with complete relief from edema, was recorded for all the 16 children.

Of the 26 patients with nutritional edema for whom serum protein determinations were done, 4 showed marked edema, 14 moderate edema, and 8 only slight edema. The relation of the degree of edema to the protein values is briefly as follows:

1. Total protein: In the 4 markedly edematous patients the total serum protein varied from 3.21 to 3.84 per cent, with an average of 3.52 per cent; in the moderately edematous patients it varied from 2.7 to 7.8 per cent, with an average of 4.66 per cent; in the slightly edematous patients it varied from 3.03 to 6.84 per cent, with an average of 4.42 per cent.

2. Serum albumin: The serum albumin varied from 1.23 to 1.89 per cent, with an average of 1.54 per cent, in the markedly edematous patients; from 1.25 to 4.03 per cent, with an average of 2.66 per cent, in the moderately edematous patients, and from 1.8 to 3.55 per cent, with an average of 2.49 per cent, among the children who showed only slight edema.

3. Serum globulin: The serum globulin varied from 1.47 to 2.46 per cent, with an average of 1.98 per cent, in the markedly edematous patients; from 1.13 to 3.77 per cent, with an average of 1.97 per cent, in the moderately edematous patients, and from 1.15 to 3.29 per cent, with an average of 1.8 per cent, among the slightly edematous patients.

4. Albumin-globulin ratio: The ratio varied from 0.67 to 1.3 per cent, with an average of 0.89 per cent, in the markedly edematous patients; from 0.78 to 2.8 per cent, with an average of 1.46 per cent, in the moderately edematous patients, and from 0.5 to 2.6 per cent, with an average of 1.44 per cent, in the children showing only slight edema.

TABLE 8.—*Values for Erythrocytes and Hemoglobin of Patients With Nutritional Edema*

Red Blood Cells	No. of Patients	Per Cent	Average Hgb. Percentage (100%=13.9 Gm.)
Under 1 million	....	.....	....
1 to 2 million	3	4.05	31
2 to 3 million	15	20.27	46
3 to 4 million	23	31.08	56
4 to 5 million	22	29.73	74
Above 5 million	11	14.86	77

For comparison, 26 patients with nutritional deficiency unaccompanied by edema had their serum protein determined (table 7). Eleven, or 42.4 per cent, had a total protein above the lower normal limit (over 6.5 per cent); 15, or 57.6 per cent, had values below that limit. Of the serum albumin values, there were only 4, or 15.38 per cent, within the normal range, the remaining 22, or 84.62 per cent, being below the lower normal limit (4.5 per cent). Four patients, or 15.38 per cent, had values above 4 per cent; 13, or 50 per cent, between 3 and 4 per cent, and 9, or 34.62 per cent, below the critical level for edema, of 3 per cent. In the serum globulin determinations, 16 patients, or 61.1 per cent, were found to have values higher than the upper normal level (2.5 per cent); the other 10 patients, or 38.8 per cent, had values within the normal range. As in the edematous patients, the type of the associated diseases did not seem to have any bearing on the serum protein values.

Erythrocyte counts and hemoglobin estimations were done for 74 children with nutritional edema while in the hospital (table 8). A majority

of them showed slight or moderate secondary anemia. Twenty-three patients, or 31.08 per cent, had erythrocyte counts of between 3,000,000 and 4,000,000, with an average hemoglobin content of 7.8 Gm. per hundred cubic centimeters; 15, or 20.27 per cent, had counts between 2,000,000 and 3,000,000, with an average hemoglobin content of 6.4 Gm.; 3 had counts between 1,000,000 and 2,000,000, with an average hemoglobin content of 4.4 Gm. There were 22 patients, or 29.73 per cent, who had counts between 4,000,000 and 5,000,000, with the hemoglobin content averaging 10.3 Gm. per hundred cubic centimeters, and 11, or 14.86 per cent, who had counts above 5,000,000, with an average hemoglobin content of 10.8 Gm.

In the cases of the 26 children with nutritional deficiency with edema and of the 26 without edema who had serum protein determinations and erythrocyte counts and hemoglobin estimations done (table 6) it is interesting to note that the erythrocyte counts and hemoglobin values appear to parallel the blood protein levels to some degree. There were more children with anemia and more with extreme anemia in the edematous than in the nonedematous group.

There was no significant relation between the degree of edema and the erythrocyte count and the hemoglobin level. In the children with marked edema cases, the erythrocyte count varied from 2,070,000 to 5,820,000, with an average of 3,890,000, and the hemoglobin content varied from 30 per cent to 86 per cent, with an average of 66.5 per cent. In the children with moderate edema, the erythrocyte count varied from 1,380,000 to 4,980,000, with an average of 3,470,000, and the hemoglobin content varied from 22 per cent to 96 per cent, with an average of 62.9 per cent. In the children who showed only slight edema, the erythrocyte count varied from 2,400,000 to 6,650,000, with an average of 4,050,000, and the hemoglobin content varied from 52 per cent to 84 per cent, with an average of 67.1 per cent.

Of the 130 patients with nutritional edema admitted and treated, 59, or 45.4 per cent, were relieved; 11, or 8.46 per cent, were improved; 4, or 3 per cent, were transferred to other hospitals or other services of the same hospital for different reasons; 5, or 3.9 per cent, were discharged against advice, and 51, or 39.23 per cent, died in the hospital (table 9).

Of the 51 patients who died in the hospital, 20, or 38.9 per cent, died within twenty-four hours after admission and 4, or 7.9 per cent, within the next twenty-four hours; thus about half of the children were dead within the first forty-eight hours after admission. It should also be noted

that those who died within the first twenty-four hours averaged 2½ years of age, which was much lower than the average age of those who died later (table 10).

In the group with nutritional deficiency without edema, 110 of the 292 patients died, making a mortality rate of 37.67 per cent, comparable to that of the edematous group. Twenty-five cases, or 22.7 per cent, died within the first twenty-four hours after admission and sixteen, or 14.6

TABLE 9.—*Results in Cases of 130 Patients With Malnutrition With Edema*

	Improved		Relieved		Discharged Against Advice		Transferred		Died in Hospital	
Age	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
0-2	2		9		1		..		17	
2-6	4		20		3		3		21	
6-12	5		30		1		1		13	
Total	11	8.46	59	45.38	5	3.84	4	3.07	51	39.2

TABLE 10.—*Mortality of 130 Patients With Malnutrition With Edema*

	Within 24 Hr. After Admission	24-48 Hr. After Admission	After 2 Days	Total
No. of patients	20	4	27	51
Per cent	38.9	7.9	53	
Average age	2½	7	5	

TABLE 11.—*Mortality of 292 Patients With Malnutrition Without Edema*

	Within 24 Hr. After Admission	24-48 Hr. After Admission	After 2 Days	Total
No. of patient	25	16	69	110
Per cent	22.7	14.6	62.7	
Average age	3	8	6	

per cent, within the next twenty-four hours; thus 41 patients, or 37.3 per cent, died within the first forty-eight hours, a smaller proportion than in the edematous group. The average age of the patients who died was higher in this group than in the edematous group. As in the edematous group, the average age of the children who died within the first twenty-four hours was lower than that of those who died later (table 11).

The main causes of death for the patients with nutritional edema who died, as detected by ordinary clinical means, were bronchopneumonia (31.38 per cent), bacillary dysentery (27.46 per cent) and noma (19.60

per cent). There were 2 patients each who died of amebic dysentery, malaria and tuberculous enteritis and 1 each who died of anaemia infantum, pulmonary abscess, beriberi, kala-azar and retropharyngeal abscess (table 12).

In the nonedematous, as in the edematous, group, bronchopneumonia (47 cases, or 42.8 per cent) and bacillary dysentery (36 cases, or 32.73 per cent) topped the list of causes of death. There were 9 deaths from noma, 8 from tuberculosis, 2 each from malaria, typhoid, Fasciolopsis buski infection and meningitis, and 1 each from Bacillus influenzae meningitis and amebic dysentery.

TABLE 12.—*Causes of Death of Patients With Malnutrition*

Disease	Malnutrition With Edema		Malnutrition Without Edema	
	No. of Patients	Per Cent	No. of Patients	Per Cent
Amebic dysentery	2	3.92	1	.90
Enterocolitis	14	27.46	36	32.73
Bronchopneumonia	16	31.38	47	42.80
Noma	10	19.60	9	8.18
Anaemia infantum (pseudoleukemia)	1	1.96	.....	.....
Pulmonary abscess	1	1.96	.....	.....
Beriberi	1	1.96	.....	.....
Malaria	2	3.92	2	1.80
Kala-azar	1	1.96	.....	.....
Retropharyngeal abscess	1	1.96	.....	.....
Tuberculosis	2	3.92	8	7.28
Typhoid	....	.....	2	1.80
Fasciolopsis buski infection	....	.....	2	1.80
Meningococcic meningitis	....	.....	1	.90
Bacillus influenzae meningitis	....	.....	1	.90
Total	51		110	

Necropsies were done on 10 of the patients with nutritional edema who died. A summary of the observations follows:

CASE 1.—*Clinical Diagnosis:* Ascariasis, bronchopneumonia, bacillary dysentery and nutritional edema.

Pathologic Observations: (1) Thrombosis of sagittal sinus and jugular vein; (2) bronchopneumonia and pulmonary edema; (3) dilated heart with hypertrophy; (4) medullary hypertrophy of adrenals; (5) bacillary dysentery of intestine; (6) 132 ascarid worms in the bowels; (7) 3 ascarides in common bile duct; (8) whipworm in cecum.

Cause of Death: Bronchopneumonia and bacillary dysentery.

CASE 2.—*Clinical Diagnosis:* Fracture of left elbow, rickets, dysentery, bronchopneumonia, pyoderma, otitis media and nutritional edema.

Pathologic Observations: (1) Brain congested with edema and flabby; (2) thyroid glands atrophic; (3) bronchopneumonia, more marked on right; (4) cloudy degeneration in spleen, liver and kidneys; (5) distention of gallbladder; (6) otitis media on both sides; (7) definite powder of sulfapyridine in muscle

in left buttock and some scraps in right, and extravasation of blood in area of injection; (8) fracture of left elbow with pus in joint; (9) small ulcer in rectum; (10) multiple furunculosis.

Cause of Death: Bronchopneumonia and dysentery.

CASE 3.—*Clinical Diagnosis:* Xerophthalmia, gluteal abscess, bronchopneumonia and nutritional edema.

Pathologic Observations: (1) Bilateral otitis media and beginning mastoiditis; (2) edema of brain and encephalomalacia; (3) edema of lungs and discrete consolidation in both lungs; (4) myocardial degeneration; (5) distention of gallbladder; (6) cloudy swelling of liver and kidneys; (7) atrophy of medullary portion of adrenals with fatty degeneration.

Cause of Death: Bronchopneumonia and sepsis.

CASE 4.—*Clinical Diagnosis:* Rickets, ascariasis, ancylostomiasis, bronchopneumonia, cancrum oris and nutritional edema.

Pathologic Observations: (1) Abscess of lung, (multiple necrotic abscess); (2) bronchopneumonia; (3) congestion of brain and dura; (4) extreme congestion of choroid plexus; (5) bilateral otitis media and mastoiditis; (6) moderate dilatation of right side of heart; (7) enlargement of spleen and dark, congested appearence; (8) extreme congestion of liver; (9) fatty degeneration of medullary portion of adrenals and cortical atrophy; (10) cloudy swelling of kidneys.

Main Cause of Death: Gangrenous noma of left side of face with multiple gangrenous abscesses of all lobes of lungs.

Contributory Cause of Death: Bilateral otitis media and bilateral mastoiditis.

CASE 5.—*Clinical Diagnosis:* Otitis media, bronchopneumonia and nutritional edema.

Pathologic Observations: (1) Extreme congestion and hemorrhage in brain, mostly at base of cerebellum; (2) atrophy of thymus; (3) bronchopneumonia of both lungs; (4) dilatation of right side of heart; (5) congestion of spleen; (6) cloudy swelling of kidneys and pyelitis; (7) atrophy of adrenal cortex.

Cause of Death: Bronchopneumonia.

CASE 6.—*Clinical Diagnosis:* Avitaminosis, bronchopneumonia, retropharyngeal abscesses and nutritional edema.

Pathologic Observations: (1) Congestion and edema of brain and dura; (2) bilateral otitis media; (3) congestion and bronchopneumonia of both lungs; (4) dilatation of and blood clots in right auricle and right ventricle of heart; (5) congestion and cloudy swelling of liver; (6) enlargement and congestion of spleen; (7) cloudy swelling of kidneys; (8) atrophy of cortex of adrenals; (9) congestion of duodenum and stomach; (10) extensive retropharyngeal abscesses; (11) fluid in peritoneum.

Cause of Death: Retropharyngeal abscesses and bronchopneumonia.

CASE 7.—*Clinical Diagnosis:* Ascariasis, avitaminosis, bronchopneumonia, bacillary dysentery and nutritional edema.

Pathologic Observations: (1) Congestion and edema of brain and dura; (2) bronchopneumonia of both lungs; (3) anemia of heart with fatty degeneration; (4) fatty changes in liver; (5) enlargement of spleen; (6) cloudy swelling of kidneys; (7) edematous mucosa of stomach; (8) ulceration of rectum, colon and cecum; (9) ascites; (10) ascariasis.

Cause of Death: Malnutrition, beriberi and bronchopneumonia.

CASE 8.—*Clinical Diagnosis:* Nutritional edema, otitis media, bronchiectasis and pulmonary.

Pathologic Observations: (1) Edema and congestion of brain and meninges: (2) bilateral otitis media; (3) bronchiectasis of lower lobe of left lung and edema, congestion and bronchopneumonia of both lungs; (4) moderate enlargement of mediastinal lymph nodes; (5) chronic passive congestion and fatty degeneration of liver; (6) slight enlargement and chronic passive congestion of spleen; (7) atrophy and congestion of kidneys; (8) whipworm and ascarides; (9) ascites, dilatation and hypertrophy of right ventricle of heart.

Main Cause of Death: Probable congenital bronchiectasis of lower lobe of left lung; malnutrition; edema, congestion and bronchopneumonia.

Contributory Cause of Death: Bilateral otitis media.

CASE 9.—*Clinical Diagnosis:* Otitis media, anaemia infantum (pseudoleukemia) and bronchopneumonia.

Pathologic Observations: (1) Draining left ear; (2) bilateral pneumonia; (3) abscess of upper lobe of right lung; (4) congestion with hemorrhages on right side of pericardium; (5) red, firm, enlarged spleen; (6) enlargement of liver; (1) congested kidneys; (8) congested and edematous colon; (9) chronic lymphadenitis.

Main Cause of Death: Abscess of right lung with bilateral bronchopneumonia.

Contributory Cause of Death: Otitis media.

CASE 10.—*Clinical Diagnosis:* Ascariasis, ancylostomiasis, gonococcic vaginitis and bronchopneumonia.

Pathologic Observations: (1) Congestion of lungs and bronchopneumonia; (2) enlargement of mesenteric lymph nodes: (3) irregular patches with nutmeg appearance in liver; (4) slightly cloudy swelling of kidneys; (5) slight atrophy of adrenals.

Cause of Death: Congestion and bronchopneumonia of lungs.

It is interesting to note that bronchopneumonia was present in all 10 as one of the main causes of death. The other causes were bacillary dysentery, sepsis, otitis media, noma, pulmonary abscess, retropharyngeal abscess, bronchiectasis and nutritional deficiency.

It was also noticed at autopsy that 5 of the 10 children showed dilatation of the right side of the heart, some with hypertrophy, and 5 showed edema of the brain. Of particular interest were the adrenal changes; 1 child had slight atrophy of the whole adrenal gland, 2 had cortical atrophy with medullary hypertrophy, 1 had medullary atrophy with fatty degeneration and 1 had medullary fatty degeneration with cortical atrophy.

COMMENT

In such a study of nutritional edema, one of the principal difficulties is the exclusion of edema caused by other diseases, mainly those of cardiac and renal origin. Renal diseases are usually rather easy to detect by ordinary clinical examinations, but cardiac conditions present greater difficulties. Functional insufficiency and sometimes even organic lesions often escape the notice of the best clinicians, and a heart

and circulatory system that are apparently normal under the amount of stress in the hospital may be really insufficient. Edema due to mild beriberi heart is especially difficult to differentiate from edema of direct nutritional origin. That a few mistakes of this kind cannot have been avoided in this study is certain.

Another point that should be explained is that the diagnosis of the presence or absence of edema in this study was based only on ordinary clinical examination, and no special method was used to determine whether the tissues of the patients contained more than the normal amount of fluid. That some of the patients classified in the nonedematous group might have had subclinical tissue edema is highly probable.

The presence of edema did not seem to modify the clinical manifestation of the general nutritional deficiency physically, mentally or psychologically except as the presence of excessive tissue fluid caused an increase of body weight. The wasting of tissue, the retardation of development, the unhealthy appearance, the fretful temperament and the peculiar involvement of teeth, skin and eyes were essentially the same regardless of the presence or absence of edema.

The presence of clinical nutritional edema did not seem in any noticeable degree to change the clinical picture of various vitamin deficiencies (A, elements of the B complex, C and D) or of the associated and complicating diseases, such as noma, parasitic infestation and infections of various sorts in different parts of the system.

Nutritional edema occurred much less frequently in the younger age groups, especially in infants under 2 years, in contrast to the high incidence of nutritional deficiency without edema in these age groups. This is thought to be due to the fact that many of the infants were fed mother's milk and the smaller children were probably taking more soybean products proportionately than the older ones.

Sex did not appear to play any part in the occurrence of edema. The condition was noted with comparable frequency in the two sexes in all the age groups, except in that below 2 years, in which there were more female edematous infants than male. This was probably due to the general tendency in China to take better care of the male than of the female infants.

That the preexisting diseases, such as those that disturb the patient's appetite, cause indigestion, impair assimilation and increase metabolism and the building-up processes probably predispose patients to development of edema is easily conceivable; but, as previously explained, the data on preexisting diseases in this study were not sufficient to permit any conclusions to be drawn.

It was difficult in many cases to determine whether the associated diseases preceded or followed the development of edema. However, as

the associated diseases may either cause or aggravate the edema as a contributory factor, or not play any part at all, it does not matter whether they preceded or followed the edema for the purposes of this study. Enterocolitis, causing a decrease of appetite, restriction of diet, impairment of digestion and assimilation and even toxin production which further impairs the nutrition of the patient, is generally believed to produce nutritional edema in some instances. It is surprising, therefore, to find that there was only a slightly larger number of patients with this disease in the edematous than in the nonedematous group (34.61 against 28.42 per cent). Probably the extreme degree of nutritional deficiency of these patients overshadowed the other contributory factors. The higher incidence of beriberi in the edematous group is thought to be due to inability to recognize the edema caused in some children by cardiac insufficiency, as suggested in the beginning of this discussion. The higher incidence of typhoid in the nonedematous group is in accord with the general experience in this hospital, as this disease usually presents itself with marked emaciation and wasting of tissue rather than with development of edema when the patients are on the old-fashioned restricted diet. The noticeably higher incidence of tuberculosis, noma and lobar pneumonia in the edematous group and the higher incidence of bronchopneumonia and rickets in the nonedematous group, as determined by clinical means, is hard to explain. Parasitic diseases either intestinal or involving the blood stream, as expected, occurred with about the same frequency in the two groups and seem not to have played any part in the development of edema.

In agreement with the findings of other investigators, the total serum protein content was lower than normal in the patient with edema, 92.31 per cent of whom had values below the normal level. This percentage is considerably higher than in the corresponding nonedematous (65.52 per cent), and the actual protein levels of most of the edematous patients were lower than those of the nonedematous children.

Generally, in accord also with the observations of other investigators, the serum albumin is the main protein factor that is affected. The serum albumin values of all the patients with edema were below the lower limit of normal, and 76.92 per cent had values below the critical level of 3 per cent. In the nonedematous group, only 86.21 per cent had values below the lower limit of normal and only 31.03 per cent below the critical level.

Lowering of the serum globulin level is not believed to play any part in the development of edema. Only 2 of the edematous patients had this value below the normal limit, and none of the nonedematous patients. Only 15.38 per cent of the edematous group had serum globulin values above the normal level, while a much higher proportion (65.52 per cent) of the nonedematous group showed increased globulin.

It is thought that the comparatively high serum globulin values of the nonedematous group may supplement some part at least of the lowered osmotic pressure of the blood, due to the lowering of serum albumin, and so may play a minor part in preventing the development of edema.

It is clear from the foregoing observations that determination of serum albumin is the most important test in the study of nutritional edema, while determination of the total protein content and of the albumin-globulin ratio, which depend partly on the globulin factor, does not give any additional information of importance.

It should be noted here that there were many patients with conditions apparently due to nutritional deficiency who had a serum albumin concentration below the critical level and no abnormality in the amount of globulin and yet had no edema which could be detected clinically. These patients showed emaciation and wasting of tissue, sometimes to a marked degree, and every feature of nutritional deficiency except edema. This is in accord with the common experience of absence of edema in most cases of typhoid and of some chronic diseases, especially of gastrointestinal origin, when the patients are put on very restricted diets by old-fashioned practitioners and hence there is reason for hypoproteinemia to develop. Further investigation in these patients' cases would be of great interest.

The type of associated diseases did not show any material effect on the protein level (total protein, albumin, globulin or albumin-globulin ratio), nor did it affect the degree of edema. However, as practically all the patients for whom protein determinations were done in this study had complicating infections of one sort or another, the normal and high serum globulin values may be partly due to these infections, suggested by other investigators.

A good many of both the nonedematous and the edematous patients with other nutritional deficiency showed slight, moderate or marked anemia, commonly known as nutritional anemia. Generally speaking, there was a greater incidence of anemia in the edematous than in the nonedematous group. Roughly, the erythrocyte count and the hemoglobin level ran parallel with the serum albumin level, which is somewhat in accord with the observations on experimental edema of Weech, Wollstein and Goettsch.[31] However, exceptions were many, and the total blood volume was not determined in these cases; hence no definite conclusion can be drawn.

The presence of tissue edema did not affect to any marked degree the gross mortality of the patients with nutritional deficiency, as there were 51, or 39.33 per cent, who died in the edematous group and 110,

31. Weech, A. A.; Wollstein, M., and Goettsch, E.: Nutritional Edema in Dog: V. Development of Deficits in Erythrocyte and Hemoglobin on a Diet Deficient in Protein, Am. J. Dis. Child. **52**:1280 (Nov.) 1936.

or 37.67 per cent, in the nonedematous group. This high mortality in both groups, as previously explained, is due to the facts that this hospital admits only patients whose condition is serious and that the people of the community from which the hospital draws its patients are in extremely poor physical condition and have a low reserve. This is well borne out by the fact that a large proportion of the deaths occurred during the first forty-eight hours.

The facts that there was a larger number of children who died within the first few hours of admission in the edematous group (47 per cent died in forty-eight hours and 38.9 per cent in twenty-four hours) than in the nonedematous group (37.3 per cent in forty-eight hours and 22.7 per cent in twenty-four hours), that the average age of the patients who died was much lower in the edematous group and that nutritional edema occurred much less frequently in infants than in older children all signify that when edema does develop in infants (below 2 years of age) it is much more serious than in older patients.

There were no differences in the clinically detected causes of death between the edematous and the nonedematous group.

It is interesting to note from the necropsies of the patients with nutritional edema that bronchopneumonia was the usual terminal condition and present in all that came under examination, and that involvement of the right side of the heart appeared in half the patients. That 50 per cent of the children had edema of the brain is another noteworthy observation. It may be part of the general tissue edema, but this is not usually thought to be the case. The changes in the adrenal glands, which occurred in half the patients, consisted mostly of cortical atrophy, in some instances of medullary hyperplasia and in some instance of medullary degeneration. Whether these changes were a part of the general wasting of tissue from nutritional deficiency or whether they played a part in the actual development of tissue edema, as suggested by Swingle [32] and his co-workers, has not been demonstrated in this study.

The explanation of the development of tissue edema in persons with nutritional deficiency is more complicated than the lack of proper pro-

32. Swingle, W. W.; Pfiffner, J. J.; Vars, H. M., and Parkins, W. M.: The Effects of Fluid Deprivation and Fluid Intake upon the Revival of Dogs Suffering from Adrenal Insufficiency, Am. J. Physiol. **108**:144, 1934; The Relation Between Blood Pressure, Blood Urea Nitrogen and Fluid Balance of the Adrenalectomized Dog, ibid. **108**:428, 1934. Swingle, W. W.; Parkins, W. M., and Taylor, A. R.: Experiments on Intact and Adrenalectomized Dogs Subjected to Sodium and Chloride Depletions by Intraperitoneal Injections of Glucose, ibid. **116**:430, 1936. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: Relation of Sodium and Chloride Levels to Alteration of Body Water in the Intact and Adrenalectomized Dog and the Influence of Adrenal Cortical Hormone upon Fluid Destruction, ibid. **116**:438, 1938.

tein ingestion. It is concerned also with the general constitution, the digestive and assimilative ability, the rate of metabolism, the physical state and the regenerative power of the serum protein of the patient. As shown in this study as well as by many other investigators, the development of edema follows low osmotic pressure in the blood due to lowering of the serum albumin factor and lack of compensation by the other proteins in the blood. But the causation is not even as simple as this. The fact that there were many patients with very low serum albumin values and without globulin compensation who did not have edema is sufficient to show that there are other factors present. It may be that the capillary walls, the tissues themselves, the endocrine system, particularly the thyroid and adrenal glands, and other unknown factors all play a part in the final development of edema.

SUMMARY

Literature on the nature and development of nutritional edema has been reviewed, and the dietary condition of the war refugees and the people of the poorer classes in Shanghai has been briefly discussed.

One hundred and thirty children with nutritional edema and 292 with nutritional deficiency without edema were studied. The presence of edema was not found to alter the clinical manifestations of the other nutritional deficiency conditions or complicating diseases. Nutritional edema was present less frequently in infants than in older children. It occurred with almost equal frequency in the two sexes. There was a higher incidence of beriberi, tuberculosis, noma and lobar pneumonia in the edematous group, and a higher incidence of typhoid, bronchopneumonia and rickets in the nonedematous group.

Serum protein determinations were made for 26 patients in the edematous group and also for 26 in the nonedematous group. The total serum protein content and especially the serum albumin level were lowered in both groups, but more in the edematous group. The serum globulin values of most of the edematous patients and of all the nonedematous patients were either normal or higher than normal. The values were proportionally higher in the nonedematous group.

The presence of edema did not alter the general mortality but appeared to parallel a higher mortality in the infants under 2 years of age.

Ten children with nutritional edema who died were submitted to autopsy. Of special interest was the frequent presence of edema of the brain and of changes in the adrenal glands.

Obituaries

FRANK LEECH, M.D.
1870–1942

Dr. Frank Leech, an emeritus member of the Academy of Pediatrics and one of its founders, died at Walter Reed Hospital in Washington, D. C., on Feb. 7, 1942.

Dr. Leech was born Jan. 14, 1870, in Prince Georges County, Md. He was educated in St. John's College, Annapolis, Md., and in Ohio Wesleyan University and received his degree in medicine from Columbian (now George Washington) University in 1891.

He served in the Medical Corps of the United States Army in 1918 and 1919 and held the rank of Lieutenant Colonel in the Medical Reserve Corps at the time of his death.

Dr. Leech was one of the pioneer pediatricians of Washington, his attraction to this specialty beginning with his service as resident physician at the Children's Hospital in 1892. His affiliation with this institution lasted for fifty years; during this long connection he served as attending physician and for twenty years was chief of staff, a position from which he retired a few years before his death. During his term in this position, Dr. Leech was largely responsible for the development of the staff from a dozen to an aggregate of over one hundred and fifty physicians now composing this body.

In January 1938, on his retirement from active service, his friends and associates established the Frank Leech Laboratory Fund to perpetuate the memory of his devotion to the interests of the Children's Hospital.

Until ill health prevented his participation in the affairs of the Academy of Pediatrics, he was a constant attendant at the general and regional meetings, where his genial presence and warm fellowship made his presence ever welcome to his many friends.

J. S. W.

HEINRICH FINKELSTEIN, M.D.
1865–1942

Heinrich Finkelstein was born in Leipzig, Germany, on July 31, 1865. He died on Jan. 28, 1942 in Santiago, Chile, where he had taken up his residence in 1939.

He began his career as a geologist, receiving his doctor's degree in this branch of science in 1888. He received his medical degree at Leipzig in 1893. After graduation he became assistant to Otto Heubner at the University Children's Clinic at Berlin. Finkelstein's work at the University Children's Clinic consisted of well studied plans of isolation, aseptic nursing and proper feeding of infants; he succeeded in reducing materially the high death rate.

He became head of the Infant Asylum and City Orphanage of Berlin in 1901, where he found the same deplorable conditions which had confronted him at the Children's Clinic. The mortality was as high as 50 per cent. However, in two years he was able to control infections in his new institution.

There at the Infant Asylum he had abundant opportunity to study the clinical manifestations of the acute digestive and nutritional disturbances. His most creative work was the classification of these disorders. Whatever the present day conception may be, his description of alimentary intoxication was brilliant and remains a classic. His system of dietotherapy has played an important part in the prevention and treatment of diarrheal diseases. His textbook on diseases of infancy is a complete presentation of the subject. He showed an active interest in the study of cutaneous diseases of young life. With Galewski and Halberstaedter he published an atlas on cutaneous diseases and syphilis, well illustrated by four-color process engravings, and he contributed other papers on the same subject.

In 1918 Dr. Finkelstein was appointed director of the Kaiser and Kaiserin Friedrich Children's Hospital in Berlin, and in this larger field he continued his clinical investigations and scientific studies. He welcomed his American students with warm cordiality, and the friendship and devotion of his colleagues in this country continued throughout his life.

Personally, Finkelstein was reserved and retiring, though he had an unusual range of knowledge in many branches of science, art and literature.

He attained a position of leadership in pediatrics during his day and generation. He will continue to be recognized as an unsurpassed clinical analyst, an outstanding investigator and scholar.

I. A. A.

News and Comment

PERSONAL NEWS

Appointments.—Dr. Francis S. Smyth, professor of pediatrics at the Medical School of the University of California, has been appointed dean of that institution.

Dr. Amos Christie, associate professor of pediatrics at the Medical School of the University of California, has been appointed assistant director of medical and health service of the American Red Cross, with offices in Washington.

Dr. Alexander Ashley Weech, of New York, has been made B. K. Rachford professor of pediatrics, University of Cincinnati Medical College; chief of staff and medical director, Children's Hospital; director, Children's Hospital Research Foundation; director of pediatrics and contagious diseases, Cincinnati General Hospital. These appointments become effective July 1.

Dr. Allan M. Butler has been made chief of the children's medical service of the Massachusetts General Hospital and associate professor of pediatrics at Harvard Medical School.

Prize Award.—Dr. Juan P. Garrahan was awarded the 1941 prize of the Academía Nacional de Medicina of Buenos Aires, Argentina, for his work on vitamin K in newborn infants.

CORRECTION

In the article by Dr. Rachel Ash entitled "Cardiac Signs in Rheumatic Infection of Childhood," in the January issue (Am. J. Dis. Child. **63**:1, 1942), the heading of table 1, on page 2, should read: "Relation of Type of Onset and Outcome of the Initial Infection in Cases of Rheumatic Infection in Childhood."

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

A Bacteriological Study of Streptococci Isolated from the Genito-Urinary Tract. Mary L. Porch, J. Bact **41**:485 (April) 1941.

Although sulfanilamide has been quite effective in controlling infections of the genitourinary tract, there are certain organisms found in these infections which are resistant to chemotherapy. The author found that streptococci and aerobacters tend to persist. Therefore, she undertook to differentiate these streptococci for the purpose of establishing a rationale for choice of chemotherapeutic agent, gaining further knowledge concerning the role of these organisms in genito-urinary infections and finally determining their importance as compared with that of other organisms commonly found under these circumstances. A study of 100 strains of streptococci isolated at random from specimens of urine was made. As a result of the microscopic, biochemical and serologic examinations of these strains, it was found that enterococci of the gamma Streptococcus faecalis type are the predominating streptococci associated with these infections. The enterococcus group as a whole consists of streptococci possessing unusual resistance to physical and chemical factors generally injurious to other types of organisms. This may lead one to feel that they should also exhibit a more marked resistance to treatment with drugs.

Stoesser, Minneapolis.

Virulence for Man of Pneumococcus Type III, with Reference to Growth Activity of Strains at 41° C. David D. Rutstein and John K. Miller, J. Bact. **41**:627 (May) 1941.

Pneumococcus type III is often isolated from the normal secretion of the respiratory tract. In these instances it may be harmless, but when this organism is the cause of pneumonia the outcome is often fatal. This fact prompted the authors to a study in which the growth at 41 C. of strains of type III pneumococci isolated from persons with pneumococcic infections of various degrees of severity was observed in relation to the outcome of the disease, the occurrence of bacteremia and the response to sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) therapy in the individual patients in this group. Sixty-three strains from 51 patients with pneumococcic pneumonia and 5 carriers of type III pneumococci, as well as 9 strains from 4 persons with pneumococcic meningitis, were investigated. They concluded that in this small series of patients with pneumonia no positive correlations were evident between the growth activity at 41 C. in vitro of the strain of pneumococcus type III isolated and the occurrence of bacteremia, the outcome of the disease or the response to sulfapyridine therapy. Only 3 of the 51 patients with pneumonia in this series had temperatures approximating 41 C. The growth activity in vitro of pneumococcus type III at 41 C. is not a factor in the determination of its virulence in this representative series of pulmonary infections in man.

Stoesser, Minneapolis, Minn.

The Use of a Single Guinea Pig for Virulence Testing. Margaret Beattie, J. Lab. & Clin. Med. **26**:863 (Feb.) 1941.

The author concludes that guinea pigs vary little in their reaction to cultures of Corynebacterium diphtheriae. She does not recommend the simultaneous injection of a control mixture of culture and antitoxin, which permits the use of a single guinea pig for several tests, since false or inconclusive reactions may occur.

Gard, Galveston, Texas.

Metabolism; Infant Feeding; Milk and Other Foods

THE PATTERN OF SERUM PROTEINS DURING ACCELERATED GROWTH. E. S. ZAWADZKI and ARTHUR H. SMITH, Am. J. Physiol. **132**:362 (March) 1941.

It has been demonstrated that animals in which increase in body weight has been restricted through lack of either food energy or the essential amino acid lysine show an unusually rapid maturation of the blood picture, as judged by the change in number of erythrocytes, concentration of hemoglobin and change in proportion of reticulocytes. Furthermore, on realimentation either with a qualitatively adequate diet or with one providing requisite energy, a more youthful blood picture again appears and the process of hematologic maturation is resumed paralleling the accelerated somatic development. Of particular interest is the increase in percentage of globulin on the restricted diet and the increase in total nitrogen and percentage of serum albumin following realimentation.

NOURSE, Cleveland.

THE CORRECTION OF DISTORTED FLUID EQUILIBRIUM IN THE PRESENCE OF VASCULAR INJURY. A. S. MINOT and KATHERINE DODD, J. Pediat. **17**:571 (Nov.) 1940.

Restoration and maintenance of a normal amount of fluid and electrolytes in the body and a normal partition of the total body water comprise an important part of adequate supportive treatment. A normal partition of extracellular water in the blood stream and interstitial spaces is possible only when an adequate amount of plasma protein is present in the blood stream. In nutritional hypoproteinemia or after a loss of plasma protein through injured capillaries there is a distortion of fluid distribution in that too little is retained in the blood stream and too much accumulates in the tissue spaces. Thus edema of the tissues and dehydration of the blood may occur simultaneously.

When plasma protein is deficient, the administration of fluid alone fails as a means of restoring an adequate volume of blood. Indeed, such measures often result in a greater loss of protein through injured capillaries. A useful early sign that fluid administration is leading to this undesirable result is the observation of a gain in weight accompanied by a progressive rise in the concentration of hemoglobin and a decrease in the concentration of plasma protein. Proper supportive treatment for such patients must include a replacement of plasma protein as well as of fluid and electrolytes. Better results in terms of retention of the replaced protein and hence of the replaced fluid in the blood stream are obtained when early liberal transfusions of plasma are combined with a conservative administration of fluid.

AUTHORS' SUMMARY.

COW'S MILK AS DIET FOR INFANTS. U. P. BASU, Indian J. Pediat. **8**:21 (Jan.) 1941.

The author presents a review of the nutritional elements in cow's milk. The need for supplementing milk diets with iron and vitamins is pointed out, and a plea is made for the better feeding of cattle.

TENNEY, Madison, Wis.

NURSING UNDER CONDITIONS OF THIRST OR EXCESSIVE INGESTION OF FLUIDS. AXEL OLSEN, Acta obst. et gynec. Scandinav. **20**:313, 1940.

The author has extensively investigated the effect of variation in fluid intake on the production of breast milk. He concludes that the amount of fluid ingested does not modify the amount of milk and that excessive fluid intake not only does not increase milk production but may in some cases act as an inhibitor.

POTTER, Chicago.

Vitamins; Avitaminoses

THE EFFECT OF THIAMIN HYDROCHLORIDE ON THE MUSCULAR DYSTROPHY OF AVITAMINOSIS E. ARTHUR D. HOLMES and MADELEINE G. PIGOTT, Am. J. Physiol. **132**:211 (Feb.) 1941.

Studies on young weanling rats in various stages of muscular dystrophy due to a diet deficient in vitamin E revealed that there was a definite response to the oral administration of massive doses of vitamin B_1 (thiamine hydrochloride). The responses of the individual rat to a definite dose varied according to the severity of the muscular dystrophy. All rats grew to maturity and have remained in good health during six months of adult life.

JOHN D. NOURSE, Cleveland.

VITAMIN K ACTIVITY OF 2-METHYL-1, 4-NAPHTHOQUININE AND 4-AMINO-2-METHYL-1-NAPHTHOL IN HYPOPROTHROMBINEMIA. E. A. SHARP, VONDER HEIDE and W. H. GOOD, J. Lab. & Clin. Med. **26**:818 (Feb.) 1941.

The authors give comparative values of several preparations with vitamin K activity. Three infants with hemorrhagic disease of the newborn were treated successfully with intravenous injections of 4-amino-2-methyl-1-naphthol hydrochloride.

GARD, Galveston, Texas.

VITAMIN K. ALTER-BUCHSCHLAG, München. med. Wchnschr. **88**:277 (March 7) 1941.

The importance of vitamin K has not been fully appreciated. The author cites a case of fatal hemorrhagic diathesis in a newborn infant in which prophylactic administration of vitamin K had been advised. The mother had also been instructed to take vitamin K during the latter part of pregnancy. This was not done because the local pharmacies did not have it. The author reviews the present concept of the function of vitamin K and the symptoms of deficiency and also calls the attention of the pharmaceutic industry to the importance of making this vitamin available to patients.

BRAHDY, Mount Vernon, N. Y.

LOCAL APPLICATION OF COD LIVER OIL IN CASES OF KERATOMALACIA. B. RADZIKHOVSKIJ, Vestnik oftal. **16**:434, 1940.

Cod liver oil was applied locally to 23 eyes of 13 children aged from 6 months to 2 years. In 9 of these children keratomalacia was the result of severe catarrh of the gastrointestinal tract; in 4 it followed measles. The lesions of the cornea varied from superficial abrasions to destruction of one third of the cornea with a descemetocele.

The therapeutic effect was noted in the first days of the treatment. In cases of severe involvement the progress of the ulceration was stopped; the time of the treatment was shortened considerably and no perforation of the cornea was observed. The local action of cod liver oil in cases of keratomalacia is favorable because of the local vitamin A insufficiency and because of the bactericidal qualities of the substance.

O. SITCHEVSKA. [ARCH. OPHTH.]

Hygiene; Growth and Nutrition; Public Health

CHILD WELFARE SOCIETIES—NEW LAWS IN BEHALF OF CHILDHOOD, ARGENTINA. VICTOR DELFINO, Bol. Inst. internac. am. de protec. a la infancia **14**:538 (April) 1941.

The author analyzes the progress attained in the development of the law with regard to child welfare and points out the cooperation given by educational, charitable and protective institutions. He states that the primary interest of the new

legislation should be the future of the child; that laws ought to be aimed toward education and crime prevention, avoiding all ideas of criminality. Simple measures of reprimand are sufficient to change in the majority of the cases the ways of the undisciplined children of beggars and of tramps; it is necessary to get an understanding of the psychology of the child by studying his life, the conditions of the environment in which he has lived and developed, etc.

The new law should abolish the idea of judging legal guilt or innocence and try to investigate the physical, psychic and mental condition of the child, thus replacing the legal judgment that punishes with the medical treatment that heals; and this treatment should be completed by a survey of the child and the family, for the purpose of determining in each case the most suitable measures.

From Author's Summary.

Maternal Insurance in Latin America. Rudolf Aladár Métall, Bol. Inst. internac. am. de protec. a la infancia **14**: 545 (April) 1941.

Starting from the fact that the Latin American countries still have a low population and that immigration and colonization are not likely to change this situation for some time the author demonstrates that protection of mothers and infants is an urgent social and economic necessity for the nationals of the New World. After studying the different ways of protecting the working women he dwells on the advantages that social insurance grants.

Maternal insurance, the usefulness of which is further increased if it is combined with health insurance, gives immediate relief to pregnant women by means of the financial aid given to them during their absence from work, which is imposed by law, by free obstetric assistance and by care in well set-up hospitals but at the same time helps to reduce infant mortality and prevent future causes of infirmities and the struggle in a reasonable way against contagious diseases, especially tuberculosis and syphilis.

From Author's Summary.

Newborn

The Treatment of Ophthalmia Neonatorum. J. S. du Toit, South African M. J. **15**:103 (March 22) 1941.

The author reports the successful treatment of ophthalmia neonatorum with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) in doses of 1/7 grain (0.0092 Gm.) per pound of body weight given three times daily (combined with irrigations with potassium permanganate, boric acid or saline solution).

Gonce, Madison, Wis.

A Case of Congenital Ichthyosis. K. Yanuma, Acta pædiat. japon. **46**:1401 (Nov. 20) 1940.

Yanuma observed a case of congenital ichthyosis, which terminated fatally on the nineteenth day after birth, occurring in a family in which two other siblings had died of the same disease. Another noteworthy feature of this family history is that the parents were cousins. Physical examination of the patient revealed a malnourished infant whose entire body was covered with angularly divided, hard and dry scales, varying in color from a light to a reddish brown. For the most part these plaques were square or oblong in shape, although a few were circular or irregular in configuration. The surface of the plaques was shiny and contained fine pittings corresponding to the openings of the sebaceous and sweat glands. Autopsy disclosed a passive hyperemia of the organs and slight alterations in the spleen, thyroid and thymus glands, although these changes were by no means specific. The most characteristic change was the pronounced keratinization of the epidermis, with numerous necrotic cells containing pyknotic nuclei, the remains of degenerating nuclei being present in the form of deep-staining granular mate-

rial lying at the transitional zone between the stratum granulosum and the malpighian rete. The author classifies ichthyosis into three types: ichthyosis congenita gravis (type I), ichthyosis congenita larvata (type II) and ichthyosis congenita tarda (type III).

KATO, Chicago.

NORMAL LEVEL OF BLOOD SUGAR IN THE NEWBORN. M. REENKOLA, Acta obst. et gynec. Scandinav. **20**:35, 1940.

The blood sugar concentration in 100 infants was estimated one-half hour, two days, five days and eight days after delivery. The average blood sugar content in the adult with the method used is 0.8 mg. per hundred cubic centimeters. The average in the newborn is between 0.03 and 0.04 mg. per hundred cubic centimeters, but much greater variability is found at birth than later in life. In none of the subjects had it reached the adult level by the time of discharge.

POTTER, Chicago.

Acute Contagious Diseases

PUBLIC HEALTH ASPECTS OF POLIOMYELITIS IN ILLINOIS. JAMES S. ALTMAN, Illinois M. J. **79**:412 (May) 1941.

The Illinois Department of Public Health's program for the control of poliomyelitis is fourfold, as follows:

1. Convalescent serum is collected, prepared and distributed over the whole state.

2. District health superintendents and qualified pediatricians and neurologists are made available as consulting diagnosticians to physicians throughout the state.

3. The serum and the diagnostic service, being financed by the State Department of Public Health, are available without charge to any patient in the state of Illinois.

4. The Division for Handicapped Children of the Department of Public Welfare provides free medical consultation services, orthopedic nursing service and hospital service to all needy patients in the state.

BARBOUR, Peoria.

STUDIES WITH H. PERTUSSIS: V. AGGLUTINOGENIC RELATIONSHIPS OF THE PHASES. EARL W. FLOSDORF, T. F. DOZOIS and ANNE C. KIMBALL, J. Bact. **41**:457 (April) 1941.

Leslie and Gardner reported in 1931 that Haemophilus pertussis is isolated from a clinical case of whooping cough as a single type. They observed that the organism could undergo on laboratory culture mediums a semireversible change through four distinct phases, each demonstrable serologically as well as on the basis of virulence and toxicity. These observations have been under dispute, and therefore the authors decided to carry out studies with H. pertussis with special reference to the agglutinogenic relationships of the phases. They found that the variation in H. pertussis is even more complex than was found by Leslie and Gardner.

Their study led them to the following conclusions: "The serological complexities within this one species emphasize the danger of comparing with finality other species of organisms with it, unless extreme precautions are taken, first, to consider thoroughly the precise relation of a given strain of H. pertussis to other strains of both homologous and heterologous phases of H. pertussis; second, to insure that the strain is not undergoing change while being studied, and third, to consider the possibility of variation within the other species of organism with which comparison is being made."

Special emphasis is placed on the fact that master strains of broad specificity maintained in stabilized desiccated form are most desirable for use in production of vaccines for whooping cough.

STOESSER, Minneapolis.

THE VALUE OF B. PERTUSSIS VACCINE IN THE PREVENTION OF WHOOPING COUGH IN A CHILD-CARING INSTITUTION. J. M. LEWIS, L. H. BARENBURG, L. GREENSPAN and B. GREENBERG, J. Pediat. **17**:585 (Nov.) 1940.

Sixty-seven young children who had been inoculated with Bacillus pertussis vaccine (Sauer) and 70 children who had not been inoculated were intimately exposed to whooping cough in a child-caring institution. The ages and conditions of exposure were comparable for both groups. Of the 67 inoculated children, 24 or 35.8 per cent had whooping cough, whereas of the 70 control children 58 or 82.8 per cent were attacked. The severity of the disease was definitely milder in the inoculated group. Three different dosages of the vaccine were employed—namely, (1) 80,000,000,000, (2) 110,000,000,000 and (3) 130,000,000,000 organisms. . . . The incidence of whooping cough was considerably lower among those receiving 130,000,000,000 organisms, 20 per cent of the children having the disease, as compared with 57 per cent in the 110,000,000,000 group and 57 per cent in the 80,000,000,000 group. . . .

Two hundred and seventy-one children were discharged from the institution from four months to four years prior to the epidemic; 120 had been inoculated with 80,000,000,000 organisms at the institution, and 151 had not been inoculated. The ages, as well as the average number of months which elapsed since discharge, were comparable for both groups. Two, or 1.7 per cent, of the inoculated children contracted whooping cough outside of the institution, whereas 22, or 14.6 per cent, of the control children developed the disease. . . .

Under conditions of household exposure, the 80,000,000,000 dosage frequently does not prevent whooping cough although it may bring about a modification of the course of the disease. Inasmuch as household exposure may be comparable to that which existed in the wards of the institution, it is therefore probable that the 130,000,000,000 dosage would prove more effective than the usual 80,000,000,000 dosage in preventing whooping cough among children intimately exposed to this disease in their homes.

FROM AUTHORS' SUMMARY.

INTRACUTANEOUS VACCINATION AGAINST SMALLPOX BY MEANS OF THE CHICK EMBRYO CULTURE VIRUS. LEWIS JACOBS and HAROLD ORRIS, J. Pediat. **17**: 626 (Nov.) 1940.

Over 800 infants and children between the ages of 6 months and 5 years were intracutaneously vaccinated with a commercial preparation of the chick embryo culture virus. A total of 290 of these children were dermally revaccinated with New York City Department of Health cowpox virus after a period of from six months to thirty months. In those initially vaccinated with 0.1 cc. culture virus mixed with blood serum from previously vaccinated donors, there were 33.3 per cent primary takes, 50 per cent accelerated takes and 16.7 per cent immune reactions. In those originally vaccinated with 0.1 cc. of culture virus mixed with blood serum from nonimmune donors, there were 10.2 per cent primary takes, 70.1 per cent accelerated takes and 19.7 per cent immune reactions. In those initially vaccinated with two injections of 0.1 cc. of culture virus, there were 4.8 per cent primary takes, 52.3 per cent accelerated takes and 42.9 per cent immune reactions. Immunity to smallpox as measured by refractoriness to cowpox may be obtained to a high degree with culture virus vaccination.

RAUH, Cincinnati.

FORMOLIZED VACCINIA VIRUS: RESULTS OF ITS USE WITH CHILDREN WHO HAD NEVER BEEN VACCINATED PREVIOUSLY. H. H. DONNALLY and A. J. WEIL, J. Pediat. **17**:639 (Nov.) 1940.

Donnally and Weil studied the immunizing effect of inactivated vaccinal virus on a group of nonimmune children ranging in age from 3 to 7 years. Purified suspensions of elementary virus bodies obtained according to Craigie's method

were inactivated with formaldehyde. Each child was given three intradermal inoculations of formaldehyde-treated vaccinia virus at weekly intervals. Four to seven weeks later each child was vigorously vaccinated cutaneously with calf lymph virus from the New York City Bureau of Laboratories. The authors believe that in children the best way to compare states of immunity to vaccinia and probably to smallpox is not by circulating antibodies, and not by size of the initial skin reaction to vaccination, but by response to revaccination with active calf virus. The results obtained in this study showed that the partial immunity obtained by the formaldehyde-treated virus was not solid or durable but was readily broken through to yield a definite jennerian vesicle following insertion of active calf virus.

RAUH, Cincinnati.

REPORT ON MEDICAL PROGRESS: SOME EPIDEMIOLOGICAL CONSIDERATIONS OF DIPHTHERIA. VLADO A. GETTING, New England J. Med. **223**:717 (Oct. 31) 1940.

There are three types of immunity to diphtheria: (1) natural immunity, (2) community immunity and (3) immunity gained by means of immunization procedures.

In the newborn, temporary passive immunity may be acquired from the mother, since the mother's diphtheria antitoxin passes through the placenta into the fetal circulation. Such passive immunity commonly disappears at the age of 6 to 9 months, but may occasionally persist throughout life.

Recent evidence suggests that natural community resistance is highest where there is a high virulent carrier rate, where the gravis type of Corynebacterium diphtheriae is prevalent, where cases of diphtheria are more frequent, where the population is dense or where these conditions have been recently current. Avirulent carriers, however, may also be responsible for producing community resistance. The lowest natural immunity is found in rural areas, where neither the disease nor carriers are found.

The Committee on Evaluation of Administrative Practices has recommended that two doses of alum-precipitated diphtheria toxoid with an interval of four weeks or a month between doses, or three doses of fluid toxoid at intervals of four weeks or a month are to be preferred for children under 10 years of age. According to the "Appraisal Form for Local Health Work" of the American Public Health Association, the immunization of preschool children is five times as important as the immunization of elementary school children. A community immunization program should be aimed at the under-5 age group, which contains the highest proportion of susceptible children. Prevention of diphtheria in infants reduces not only morbidity but also mortality, for case fatality is highest under 2 years of age and decreases with increasing age.

GENGENBACH, Denver.

SULFANILAMIDE IN THE MANAGEMENT OF ACUTE STREPTOCOCCAL, PARTICULARLY SCARLATINAL, INFECTIONS OF THE UPPER RESPIRATORY TRACT. CONRAD WESSELHOEFT, New England J. Med. **224**:221 (Feb. 6) 1941.

Scarlet fever offers an excellent opportunity to investigate the action of sulfanilamide. In eight clinical studies, comprising a total of 1,239 patients tested against 1,220 controls, this drug was given as a routine by mouth throughout the febrile stage in the accepted dosage. It failed to benefit them in any way in the eruptive stage.

However, if scarlet fever antitoxin or convalescent serum is administered within the first twenty-four hours, one usually obtains a dramatic drop in the fever, a blanching of the rash and a distinct improvement in the inflamed throat.

The next question is whether sulfanilamide can prevent pyogenic complications. In four of these clinical tests administration of the drug was continued only during the febrile stage. The combined results of the tests (474 treated patients; 587 controls) showed no diminution in the incidence of complications. In England,

a combination of the drug with scarlet fever antitoxin was used in 317 cases and controlled by 329 cases in similar age groups treated with antitoxin alone. Again no diminution of the complications occurred as a result of the sulfanilamide, in spite of this additional antibody supply.

In contagious diseases not of streptococcic origin hemolytic streptococci are, nevertheless, frequently the cause of complications. Thompson and Greenfield used sulfanilamide in the treatment of measles and of whooping cough in the usual dosage, followed by a maintenance dose for carefully controlled age groups. The drug showed no effect whatever on the eruptive phase of measles or on the paroxysmal manifestations of pertussis, but the incidence of bronchopneumonia was reduced in both diseases in the drug-treated series. There was a material reduction in the incidence of otitis media in the 400 patients with measles who were given sulfanilamide.

Sulfanilamide is exceedingly valuable in reducing the mortality that follows the onset of serious complications. The majority of the deaths from scarlet fever today are due to the end results of pyogenic infections, particularly of the mastoid cells, in which the blood stream or the meninges become invaded. The death rate for these two serious complications, bacteremia and meningitis, has been markedly reduced.

GENGENBACH, Denver.

TREATMENT OF MENINGOCOCCAL MENINGITIS. EDWIN H. PLACE, New England J. Med. **224**:234 (Feb. 6) 1941.

The author first reviews the literature on the use of antimeningococcus serum and antitoxin; then he reports on the use of serum and sulfanilamide; and finally he discusses the use of sulfanilamide alone.

Among the most striking effects of sulfanilamide treatment are the rapid subsidence of symptoms and of the spinal fluid pleocytosis and the speedy disappearance of the organisms from the blood and the spinal fluid, usually in twenty-four hours.

Relapses and recurrences after treatment with sulfanilamide have been reported in only 0.5 per cent of the cases, and these have occurred without exception when there has been inadequate treatment. The drug should promptly reach a level in the spinal fluid of 5 to 10 mg. per hundred cubic centimeters, although lower concentrations are often effective.

Oral administration is entirely satisfactory; if vomiting occurs, the drug may be given subcutaneously in 0.8 per cent solution or intrathecally.

Meningococcemia has disappeared promptly following sulfanilamide treatment, even in patients found resistant to serum therapy.

GENGENBACH, Denver.

TWO MILK-BORNE EPIDEMICS TRACEABLE TO A SINGLE DAIRY (BACILLARY DYSENTERY OUTBREAK). HOLLIS S. INGRAHAM, New York State J. Med. **40**:1135 (Aug. 1) 1940.

In August and September 1935, an outbreak of bacillary dysentery occurred in the village of Red Creek, N. Y., a town of 600 inhabitants. One hundred and thirty-four cases occurred, in 42 of which the patients were under 15 years of age. The symptoms were those of mild bacillary dysentery, and in 12 cases dysentery bacilli of the Flexner type were obtained. There were no deaths. A house to house canvass revealed that all the patients had used milk from one dairy, and it seemed likely that the dairyman had been in a temporary carrier state and had contaminated the milk.

In February 1936 an epidemic of scarlet fever occurred in the same town. There were 73 cases, in 22 of which the patients were less than 15 years of age. The disease was not severe. Cultures of hemolytic streptococci were obtained from the throat. There were 3 deaths. This epidemic was traced to the same milk dealer. Hemolytic streptococci of group A of the Lancefield classification

were isolated in milk from this dairy. A cow was found to be suffering from acute mastitis, but no clue to a human source was obtained. The village then passed an ordinance requiring pasteurization of all milk.

AIKMAN, Rochester, N. Y.

INFREQUENCY OF TOXOID REACTIONS IN 11,326 SCHOOL CHILDREN. JACOB H. LANDES, New York State J. Med. **40**:1594 (Nov. 1) 1941.

No alarming reactions were observed after the administration of diphtheria toxoid to 11,326 school children. Reactions are more frequent in children 9 years of age and over than in younger ones. Reactions requiring home visits occurred in only 0.33 per cent of those inoculated.

AIKMAN, Rochester, N. Y.

SUMMARY OF COMMUNICABLE DISEASES, Pub. Health Rep. **56**:481 (March 14) 1941.

For the period from Jan. 26 to Feb. 22, 1941, the incidence of influenza decreased in almost all sections, although it remained considerably above the median average. The incidence of measles doubled during the same period. That of poliomyelitis was 20 per cent above the seasonal expectancy, and that of whooping cough, 40 per cent. Diphtheria, meningococcic meningitis, scarlet fever, smallpox and typhoid fever all had an incidence below the median prevalence for the period. The mortality rate from all causes was 13.6 per thousand, which is slightly above the average.

SANFORD, Chicago.

EXPERIMENTAL POLIOMYELITIS: THE USE OF A VARIETY OF LABORATORY TECHNIQUES IN EFFORTS TO ESTABLISH SEVEN STRAINS OF POLIOMYELITIS VIRUS IN THE COTTON RAT. S. D. KRAMER, W. N. MACK and A. T. HIMES, Pub. Health Rep. **56**:581 (March 21) 1941.

The authors used 7 strains of virus, 257 eastern cotton rats and 187 white mice. They were unsuccessful in establishing any of the 7 strains of virus in either the eastern cotton rat or the white mouse.

SANFORD, Chicago.

MUSCLE PATHOLOGY IN ANTERIOR POLIOMYELITIS: ITS RELATION TO FUNCTION. H. E. HIPPS, South M. J. **34**:135 (Feb.) 1941.

The author states that there is a possibility of improving the strength of a muscle by an operative attack on the individual muscle itself. The type of surgical procedure will depend on the existing pathologic condition and cannot be definitely standardized.

The author believes that the pathology of the muscles in infantile paralysis is a subject worthy of a great deal more continued and intensive study, since an accurate knowledge of the distribution of pathologic changes may make it possible to restore strength to many muscles that can derive no further benefit from bracing and physical therapy.

SCHLUTZ, Chicago.

CEREBROSPINAL MENINGITIS. N. MUTCH, Guy's Hosp. Gaz. **54**:282 (Oct. 5) 1940.

The only effective prophylaxis against cerebrospinal meningitis, according to Mutch, consists in free ventilation and the avoidance of overcrowding. Since the survival time of the isolated meningococcus is short, the disease can be contracted only by close association with some one already infected. It was found that the carrier rate of infection could be reduced in dormitories to 5 per cent by spacing beds 3 feet (90 cm.) apart, as compared with a 20 per cent rate with 1 foot (30 cm.) bed interspacing and a 29 per cent rate with a 9 inch (22 cm.) bed interspacing. In the treatment of cerebrospinal meningitis, lumbar puncture and

antimeningococcus serum have been replaced by sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) with marked results. Here the superiority of one drug over the other has not yet been determined. In 5,306 cases reported during the war years of 1914 to 1918 mortality was as high as 65 per cent; in 5,093 cases reported for the first six months of 1940 the death rate was only 20 per cent. Lumbar puncture is performed only at weekly intervals or when definite signs of increased intracranial pressure are observed. The dose, administered in approximately equal quantities for the two drugs, ranged from 3 Gm. for infants to 9 Gm. for adults (down to 15 years). It was given daily for a week in six doses spaced four hours apart in order to maintain a uniform concentration in the body tissues, but allowance was made for adjustments in severe attacks with supplementary intravenous injections of sulfapyridine sodium. Comatose patients were given the drug in powdered form in suspension through a stomach tube. Intramuscular injections were found impracticable for a number of reasons. In view of the frequent occurrence of adrenal hemorrhage in cases of septicemia rapidly terminating fatally, vitamin C, citrus fruits and adrenal cortex extract are tentatively suggested as agents for saving life. Since rapid dehydration occurs in unconscious pyrexial patients, a copious fluid intake is recommended, by stomach or rectal tube or by an intravenous drip of dextrose-saline solution. The author discusses the nature of the infective organism, its path of invasion, the spread of the infection, the clinical varieties of the disease and complications, such as the common occurrence of arthritis. A preparation that is inexpensive, soluble and susceptible of being administered rectally to unconscious patients or to those with troublesome cerebral vomiting is a desideratum.

J. A. M. A.

EXPERIMENTAL MEASLES: TRANSMISSION OF THE DISEASE TO MONKEYS, FAILURE TO TRANSMIT MEASLES TO RABBITS, CULTIVATION OF THE VIRUS ON THE CHORIO-ALLANTOIC MEMBRANE. E. W. HURST and B. COOKE, M. J. Australia **1**:323 (March 15) 1941.

Inoculation by a combination of routes, of defibrinated blood and filtered nasal washings from cases of human measles led to symptoms of measles in Macaca mulatta, Macacus radiatus and Cebus fatuellus. Similar experiments with Macacus irus, Macacus maurus and Cynopithecus niger gave negative results.

The virus was thus isolated only at the height of the epidemic. Months later, when the epidemic was nearly over, attempts to transmit the disease to monkeys were unsuccessful. Repeated passages of the virus intramuscularly led always to loss of virulence except in the case of splenectomized monkeys. General irradiation of monkeys with roentgen rays did not increase their susceptibility.

Frozen defibrinated blood retained its infectivity for ten but not for twenty-three days. Dried in the frozen state and stored in vacua, infected tissues were avirulent after one hundred and fifty-two to two hundred and ninety-four days.

Inoculations into rabbits, with or without splenectomy, gave negative results. It is probable that the virus may be grown on the chorioallantoic membrane of developing hens' eggs, but without the production of characteristic lesions which would render the method of use in further studies.

A case of probable laboratory infection from a monkey is recorded.

GONCE, Madison, Wis.

BEHRING'S SERUM 50 YEARS OLD. W. SCHMIDT-LANGE, München. med. Wchnschr. **87**:1336 (Nov. 29) 1940.

On Dec. 4, 1890 Behring and Kitasato announced that they had succeeded in immunizing animals against diphtheria and tetanus. The author gives a historical sketch of Behring's life and discusses his many outstanding scientific contributions.

BRAHDY, Mount Vernon, N. Y.

EXPERIENCES IN THE MENINGITIS EPIDEMIC IN HUNGARY DURING 1940. F. NODOSY, München. med. Wchnschr. **87**:1350 (Dec. 6) 1940.

During the first eight months of 1940 there were 3,035 cases of epidemic meningitis reported in Hungary, with a mortality rate of 18.5 per cent. This is in contrast to previous rates, which varied between 20 and 80 per cent. The decrease is due to the introduction of chemotherapy. The author treated 57 patients, with a fatality rate of 12.3 per cent. Best results were obtained by combining serotherapy and sulfapyridine. One gram of sulfapyridine was given four times a day for four or five days. Sulfathiazole also gave good results, but more of the drug was required and it was therefore less economical. Serum was considered an adjuvant in the treatment. In some cases it was administered intrathecally in daily doses of 20 cc.; in others it was given intravenously on alternate days. Complete deafness developed in 3 cases, acute encephalitis in 1 and hemocephalus internus in 1. About half of the patients showed transient electrocardiographic changes.

BRAHDY, Mount Vernon, N. Y.

A CASE OF EPIDEMIC MENINGITIS WITH TUBERCLE BACILLI IN THE SPINAL FLUID. O. BAUR, München. med. Wchnschr. **88**:47 (Jan. 10) 1941.

With the increase in epidemic meningitis in all parts of Germany there have been reports of unusual experiences with this disease. Baur reports the case of a girl, aged 14 years, in which both meningococci and tubercle bacilli were isolated from the spinal fluid. The meningococci were found in the spinal fluid at the time of admission to the hospital. Intravenous and intrathecal serotherapy was administered. Iridocyclitis developed on the fourth day. The spinal fluid on the eleventh hospital day contained 1,600 cells; tubercle bacilli, but no meningococci, were isolated by culture. Four days later tubercle bacilli were found on direct smear of the spinal fluid. In another week the spinal fluid was sterile and the patient recovered. A follow-up examination seven months later showed a perfectly well child. Roentgenograms of the lungs failed to reveal evidence of tuberculosis.

BRAHDY, Mount Vernon, N. Y.

ACUTE ANTERIOR POLIOMYELITIS AND WAR SERVICE INJURY. H. NASE, München. med. Wchnschr. **88**:293 (March 14) 1941.

Nase reports the case of a 26 year old soldier who was admitted to the hospital with fever, occipital headache, backache, inability to sit up or to turn in bed and respiratory difficulty.

Two days before admission he had slipped and injured his head while attempting a high jump. The fall had not caused loss of consciousness but had been followed by a headache. The following day he felt well enough to take part in a cross country run of several miles. He was more fatigued than usual when he finished the run. That night he vomited and had a headache.

The paralysis was progressive, and the respiratory difficulty increased. He died nine hours after admission to the hospital. The diagnosis of acute anterior poliomyelitis was made at autopsy.

The author discusses the relation of overexertion and poliomyelitis. He cites several reports in the literature of persons who had a fulminating course following some strenuous activity. They were sporadic cases, and Nase postulates that the normal resistance is impaired by fatigue. BRAHDY, Mount Vernon, N. Y.

NASAL AND ORBITAL COMPLICATIONS OF SCARLET FEVER. STEFAN KREPUSKA, Ztschr. f. Hals-, Nasen- u. Ohrenh. **46**:175, 1939.

In the two year period of 1937-1938, a study of 797 cases of scarlet fever revealed severe sinal complications in 61. In 28 of these, the sinal condition was associated with some orbital involvement. The maxillary and the ethmoid sinuses

were the most frequently involved. Since the skeletal arrangement of the nose and face is in children composed at many sites of cartilage, connective tissue and mucous membrane, an infection can readily involve these areas, and since the suture lines are not completely closed, the infection can readily spread from the sinus to the orbit.

The author advises conservative treatment in the early stages. This should comprise shrinkage, suction, irrigation, fracture of the middle turbinate and antral puncture. However, if these conservative measures fail to produce a subsidence of symptoms within twenty-four to forty-eight hours, radical surgical intervention should be considered. Depending on the amount of involvement, the following procedures are indicated: the Caldwell-Luc operation, ethmoidectomy or the external frontal sinus operation (Killian). He believes that in children intranasal surgical operations are less effective than the more radical procedures. In the series of 61 cases, he reported only 1 death following any of these procedures.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Acute Infectious Diseases

BANANA DIET IN BACILLARY DYSENTERY: A PROCTOSCOPIC STUDY. L. A. BLOCK and ALEXANDER TARNOWSKI, Am. J. Digest. Dis. **8**:3 (Jan.) 1941.

This study is somewhat different in that proctoscopic examination was performed on each of the 127 patients with bacillary dysentery before any treatment was instituted. The diagnosis was substantiated in a large percentage of cases by positive bacteriologic and serologic observations. Subsequent sigmoidoscopic examinations were made periodically to determine the character of stool and the appearance of the mucosa of the rectum and sigmoid.

Of the 127 patients, 65 were on banana diets and 62 on control diets. Observations of symptoms, weight, temperature and appearance of the rectum and sigmoid and the mortality and morbidity rate of the patients in comparable groups tend to indicate that the use of bananas is advantageous in bacillary dysentery.

MORRISON, Savannah, Ga.

TETANUS AND THE PROPHYLACTIC USE OF ANTITOXIN FOLLOWING INJURIES OF THE EYE. D. G. COGAN, Am. J. Ophth. **22**:1365 (Dec.) 1939.

After a discussion of the use of tetanus antitoxin Cogan draws the following conclusions.

"The development of tetanus following ocular injury is usually, if not always, associated with panophthalmitis. This panophthalmitis, however, is caused by organisms other other than B. tetani. Enucleation does not offer any assurance against the development of generalized tetanus even when performed during the first 24 hours after the injury, and apparently does not affect the mortality rate.

"Tetanus following ocular injury is obviously a rare catastrophe, for it has been reported in the literature only 20 times. That this relative infrequency is not simply the result of prophylactic antitoxin is apparent from the fact that there were only 14 case reports of the condition in the entire world literature before the days of prophylactic antitoxin. In view of this relative infrequency and of the danger incident to the administration of serum, it might seem that prophylactic use of antitoxin is never indicated following ocular injury. But practically all those injuries that did result in tetanus had been caused by objects associated with horses directly or with ground probably contaminated by manure. It would seem justifiable, therefore, to give antitoxin in those cases in which there is a history of such contamination. These would actually comprise a very small percentage of the total number of cases of injury to the eye. While a single prophy-

lactic injection of 1,500 units is probably adequate, repetition of this once during the first week would be justified as an added precaution."

W. S. Reese. [Arch. Ophth.]

A Device for the Diagnosis of Enterobius Infection. Clarance F. Graham, Am. J. Trop. Med. **21**:159 (Jan.) 1941.

The author describes a simple, quick method of trapping the eggs of Enterobius vermicularis on the adhesive surface of a specially prepared transparent cellulose tape, which is then placed on a microscope slide and examined as though it were an ordinary slide and cover glass preparation.

Burpee, Augusta, Ga.

Treatment of Brucellosis with Brucella Antigens. W. R. Castoneda and C. C. Cardenas, Am. J. Trop. Med. **21**:185 (March) 1941.

The authors report 35 cases of brucellosis treated with brucella antigens. They noted a rapid and sustained improvement without reactions in a number of their cases. No deaths occurred in their cases. They concluded that, while their results were not as good as those reported by some workers, the use of the antigen in the treatment of brucellosis is advisable.

Burpee, Augusta, Ga.

Paralytic Accidents Due to Rabies Vaccine. Lorne W. Mason and Rodger S. Dille, Illinois M. J. **79**:414 (May) 1941.

A case of multiple neuritis due to rabies vaccination is reported. Paralytic accidents due to antirabic treatments are discussed. Treatment in cases in which they occur is suggested.

Barbour, Peoria.

Tetanus in a Serum-Sensitive Patient Successfully Treated with a New Despeciated Antiserum. Martin Schaeffer and Gordon B. Meyers, J. Allergy **12**:188 (Jan.) 1941.

A patient with tetanus who was sensitive to commercial antitoxin was treated successfully with a despeciated antitoxin—an equine tetanus antitoxin partially digested with taka diastase. There was a slight reaction to the antitoxin in the form of chills. However, the patient, when tested intradermally approximately a year later, gave the following reactions to the two antitoxins:

New tetanus antitoxin, 0.1 cc. intradermally: wheal 1.2 cm. and erythema, 3.0 cm.

Regular tetanus antitoxin, 0.1 cc. intradermally: wheal 1.8 cm. and erythema, 6.0 cm.

Hoyer, Cincinnati.

A Complex Vaccine Against Influenza A Virus. Frank L. Horsfall Jr., Edwin H. Lennette and Elsmere R. Rickard, J. Exper. Med. **73**:335 (March) 1941.

The authors report evidence of a very potent influenza A vaccine, prepared from chick embryo inoculated with both influenza A virus and the X strain of canine distemper virus. The authors are unable to explain the action of the canine distemper virus in increasing the antigenicity of the vaccine.

Billington, Seattle.

Active Immunity to Influenza Virus in the Mouse. Ronald Hare, J. Immunol. **40**:267 (March) 1941.

Evidence is presented that, provided sufficient vaccine is administered, a very high degree of immunity to both homologous and heterologous strains of influenza

may be produced in the mouse. The author suggests that these results offer some hope for practical immunization procedures among the whole population.

BILLINGTON, Seattle.

ROCKY MOUNTAIN SPOTTED FEVER: AN ANALYSIS OF EIGHTEEN CASES IN CHILDREN. HARRY A. ONG and JOSEPH F. RAFETTO, J. Pediat. **17**:647 (Nov.) 1940.

An analysis of 18 cases of Rocky Mountain spotted fever observed in the Children's Hospital, Washington, D. C., over a period of nine years is presented. The ages ranged from 9 months to 10 years. There were 15 white and 3 Negro children; 10 were girls and 8 were boys. Twelve lived in rural districts in Maryland, and 3 came from Virginia. In 10 cases a tick was found on the body either preceding or early in the illness. A characteristic rash was present in every case. In 11 cases the rash appeared from the third to the fifth day of illness. In one-half the cases the fever was of the continuous type; in the others it was remittent. Irritability was a common symptom. The agglutination of Proteus OX-19 was positive in the majority of the cases, usually in the latter part of the second week and in the third week. The leukocyte count showed a wide range. Three deaths occurred, giving a mortality rate of 16.6 per cent. The treatment given was largely symptomatic and supportive. It is of interest that many physicians advise against transfusions and intravenous fluids in this disease, for patients receiving this form of therapy do not do so well as those who do not receive this therapy.

RAUH, Cincinnati.

RHEUMATIC HEART DISEASE: PATHOGENESIS AND ETIOLOGY IN THEIR RELATION TO THERAPY AND PROPHYLAXIS. HOMER F. SWIFT, Medicine **19**:417 (Sept.) 1940.

The author discusses the pathology of this disease. With the articular and cardiac lesions, he points out, trauma, excessive motion and functional strain are important elements in localization of the rheumatic injury. From a therapeutic standpoint excessive motion of the heart can be reduced by prolonged rest and also by antipyretic drugs, which indirectly reduce the heart rate. Reduction of 10 beats per minute results in a total of 14,000 fewer per day.

The author states that hemolytic streptococci bear a more intimate relationship to the disease than any other known pathogenic agent. Rheumatic subjects apparently do not behave in the same way toward streptococcic infections of the respiratory tract from an immunologic standpoint as do persons not suffering from rheumatism.

He states that sulfanilamide has no effect on rheumatic fever once a streptococcic infection has occurred; however, he cites the studies of Cobrun and Moore, which suggest that prophylactically, when given over a long period, sulfanilamide almost entirely prevented rheumatic recurrences. He points to the necessity for great caution in giving sulfanilamide over long periods.

LIMPER, Louisville, Ky.

RECOVERY FROM ACUTE RHEUMATIC FEVER WITHOUT PERMANENT CARDIAC DAMAGE. MORTON G. BROWN and LOUIS WOLFF, New England J. Med. **223**:242 (Aug. 15) 1940.

This study is based on 175 consecutive, unselected patients admitted to the wards of the Beth Israel Hospital with acute rheumatic fever, with or without chorea. After the acute attack, they were seen in the cardiac clinic of the outpatient department on repeated occasions over periods varying between four and eleven years. In arriving at the final opinion the authors took into consideration the physical examination, the electrocardiogram, the roentgenogram of the heart taken at a distance of 7 feet (2.1 meters) and the fluoroscopic examination for chamber enlargement.

Although the average age (13½ years) at the time of the first attack was somewhat higher in this series than in those reported elsewhere, 35 patients were under 10 at the time of their first rheumatic infection.

The authors' conclusions are as follows:

"Fifty per cent of a group of 175 patients with acute rheumatic fever showed no evidence of heart disease after follow-up periods averaging seven years.

"There is no constant relation between the severity of the illness or the number of recurrences and the development of cardiac damage.

"Patients who show no permanent organic heart changes following the first attack of rheumatic fever are prone to escape permanent injury despite further attacks.

"The final evaluation of the state of the valves must be delayed for several years after an attack of rheumatic fever."

GENGENBACH, Denver.

PNEUMOCOCCAL CROSS-INFECTIONS IN THE HOME AND HOSPITAL. HENRY A. HOLLE and JESSE G. M. BULLOWA, New England J. Med. **223**:887 (Nov. 28) 1940.

The authors show that pneumococcic pneumonia is an acute communicable disease, for cross infections occur both in the home and in the hospital ward. They present 5 examples of cross infection among families in the home and 4 which developed in the wards of the hospital.

In the S family, type 2 pneumococcus pneumonia occurred in a younger sister (5 years old) within three days after the first patient was hospitalized, and within five days of the onset of the disease in the first patient (7 year old boy).

The 7 members of the C family lived in a small five room apartment. S. C. (case 1), a 9 year old boy, slept with H. C., the only member of the family to escape infection with the type I pneumococcus. S. C. had a cough with fever, and because he appeared so sick he slept with his mother, A. C. (case 2), until he was admitted to the hospital. A. C. then had chills, fever and a cough, and was finally admitted to the hospital with bacteremia.

S. C. was taken to the hospital by L. C. (case 3), an older sister (18 years old). While waiting for S. C. to be admitted, she held his head in her lap. That night she had chills and slept with her mother, A. C., who was already ill. She was admitted with A. C.

C. C. (case 4) nursed his wife, A. C., and daughter, L. C., after working hours until he became ill. He was admitted to the hospital.

D. C. (case 5), a 6 year old girl, and R. S. (case 6), a 3 year old sister, slept in the same bed. Both were admitted to the hospital with a type I pneumococcus pneumonia.

Family Su presents an instance of type 5 pneumococcus pneumonia in a father followed one day later by a similar infection in the son (11 years old).

The P family presents an interesting history of twin brothers, 3 years old, who were admitted to the hospital at the same time with an infection of the upper respiratory tract and on the following day had pneumonia due to the type 5 pneumococcus.

C. W. (case 2), the mother, slept with J. W. (case 1), a 9 year old girl, until the latter was admitted to the hospital. Both had a type I pneumococcus pneumonia.

The author also describes in detail 4 cases of apparent contact infection occurring in the hospital.

GENGENBACH, Denver.

PHENOTHIAZINE AS AN ANTHELMINTHIC IN THREADWORM AND ROUNDWORM INFECTIONS. PHILIP MANSON-BAHR, Lancet **2**:808 (Dec. 28) 1940.

Phenothiazine (thiodiphenylamine) is a thiazine dye and the parent of a large number of such substances, including methylene blue (methylthionine chloride).

This drug has given consistently satisfactory therapeutic results in Oxyuris vermicularis infections, especially in children. For children under 8 years a dose of 2 Gm. daily for seven days appears to be sufficient, and half this dose for children under 4 years. No disagreeable after-effects have been noted, and no dietetic restrictions have been required. The dye is mostly excreted in the urine.

The drug also proved effective in roundworm infection in 7 native patients (6 Indians and 1 Egyptian). It seemed to have no effect on whipworms or hookworms.

LANGMANN, New York.

BONE MARROW CHANGES IN ACUTE INFECTIONS AND THE EFFECTS OF SULPHONAMIDES ON THE MARROW. T. E. WILSON, M. J. Australia **1**:257 (March 1) 1941.

Patients in whose peripheral blood sulfanilamide and its derivatives produced little or no effect showed no alterations in the marrow attributable to the sulfonamide therapy. In acute infections the macropolycytes occur in the marrow more often than in the peripheral blood. "Toxic" granules are more numerous in the myelocytes than in the mature neutrophile cells of the marrow in acute infections. Nuclear abnormalities may occur in the neutrophile cells of the marrow during the preparation of smears from marrow curettings emulsified in serum. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was administered to four patients suffering from acute leukemia without the production of any alteration in the clinical condition, the blood, the bone marrow or the prognosis.

GONCE, Madison, Wis.

STUDIES IN INFLUENZA. R. SCHAFFER and B. G. SHAPIRO, South African M. J. **15**:83 (March 8) 1941.

During an epidemic of influenza at the Military Camp, Premier Mine, approximately 30 per cent of the men contracted the disease. The onset seems to have been related to a sudden fall in maximum temperatures, without change in the minimum temperatures, that occurred between July 2 and July 6, 1940. Susceptibility to infection was not affected by age or by dusty surroundings. The incubation period was two to three days. The epidemic lasted seven weeks in each regiment, irrespective of when it began, and subsided with the development of immunity in the susceptible men rather than with decrease in virulence of the virus. Clinically there was a tendency to relapse of short duration on the fourth or fifth day after the original fever had subsided, and to repeated relapses of fever over a period of about six weeks associated with "wandering pneumonia." The mortality rate was negligible. Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was of no value in shortening the duration of the initial fever, had no special virtue to compensate for its frequent toxic effects and tended to favor relapses (because of an accentuation of the leukopenia, which further handicapped the defensive reactions of the body).

GONCE, Madison, Wis.

INTESTINAL PARASITE INFECTIONS OF MAN IN CHENGTU AND ITS VICINITY. K. CHANG and C. C. LIN, Chinese M. J. **58**:570 (Nov.) 1940.

This report comes from the joint work of a doctor of philosophy and one of medicine; from the Departments of Biology and Public Health of Cheeloo University, and the Pathological Laboratory of the United University Hospital of Chengtu, in West China. There were 2,896 specimens examined, and it was a significant finding in the epidemiology of human intestinal parasites that the incidence of protozoan parasites is low, even in an environment favorable for dissemination. In the group of school children studied the rate of infection with Endamoeba

histolytica was 0.88 per cent, and in a group of adults most of whom were over 45 years old the rate was 1.52 per cent, which must be considered low. In young soldiers the incidence was found to be 9.1 per cent.

Roundworm had the highest incidence in school children (82.49 per cent), with a lower incidence in each of three groups of adults.

The incidence of hookworm was in general low. In soldiers, who usually go barefoot, it was 34 per cent. Pinworm is rare. Other species of parasites appearing occasionally are reported.

NEFF, Kansas City, Mo.

THE NEUTRALIZATION OF JAPANESE ENCEPHALITIS VIRUS BY SERUM. C. H. HUANG, Chinese M. J. **59**:34 (Jan.) 1941.

This author previously took part in a study of 6 proved cases occurring in China during 1939. His present studies on neutralization tests have led him to believe that the demonstration of neutralizing antibodies in the serum of a patient does not in itself furnish conclusive proof that the virus was the cause of a given recent illness. As shown by Rivers and Scott in their study of lymphocytic choriomeningitis, only in those cases with negative serum reactions early in the disease and positive reactions later can it be regarded as proved that the virus is the cause of the disease.

NEFF, Kansas City, Mo.

Chronic Infectious Diseases

CHANGE IN SEDIMENTATION RATE OF RED BLOOD CORPUSCLES IN TUBERCULAR DISEASES OF THE SYSTEM. N. K. BASU, Indian J. Pediat. **8**:30 (Jan.) 1941.

It was found that in tuberculosis sedimentation rate curves over a six hour period were found to be more rapid and to have a characteristic shape. The rate varied with the stage of the disease, but the shape of the curve remained characteristic. The author regards the shape of the curve as more reliable than tuberculin tests on the skin. With high doses of vitamin C there is tendency for the curves to approach normal, but it remains to be seen if there is any corresponding effect on the clinical course of the disease.

TENNEY, Madison, Wis.

LATE HEREDITARY SYPHILIS OF THE TESTICLES. J. GAZZOLO, Rev. méd. latino-am. **25**:1367 (Sept.) 1940.

The author reports a case of a boy of 14 years with a history of bilateral interstitial keratitis who was brought to him because of a firm, uniform, painless enlargement of both testicles. The child presented typical Hutchinson teeth and opacities of the corneas. The boy was given mercury and iodides by mouth and intramuscular injections of a bismuth compound, and there were rapid improvement in the testicular condition and complete return to normal.

LEIFER, New York. [ARCH. DERMAT. & SYPH.]

Diseases of Blood, Heart and Blood Vessels and Spleen

RHEUMATIC PERICARDITIS WITH EFFUSION TREATED WITH SALICYLATES. ERNST P. BOAS and MAX ELLENBERG, J. A. M. A. **115**:345 (Aug. 3) 1940.

The authors found that salicylates not only relieved the exudative process of rheumatic fever and the accompanying pain but reduced the exudate of rheumatic pericarditis. The proliferative action of the rheumatic process manifested in myocarditis and endocarditis does not seem to be influenced.

Reports of 2 cases are included. Both patients had prompt relief from severe pericardial effusions.

HEERSMA, Kalamazoo, Mich.

THE DETERMINATION OF BLOOD VELOCITY BY LOBELINE. FRANK V. PICCIONE and LINN J. BOYD, J. Lab. & Clin. Med. **26**:766 (Feb.) 1941.

On 95 patients the authors used alphalobeline for the determination of the "circulation time." They found no toxic symptoms in these patients and they think this compound is better than decholin or saccharin. The end point is a tickling sensation in the throat, which may or may not be accompanied by a cough.

GARD, Galveston, Texas.

REPORT OF A CASE OF CONGENITAL ABSENCE OF THE SPLEEN AND CHRONIC AMNIOTIC FLUID PNEUMONIA. RICHARD L. NELSON and D. R. VENABLE, J. Lab. & Clin. Med. **26**:772 (Feb.) 1941.

The authors report the case of a child who died at the age of 14 months. This infant did very poorly during life, was cyanotic most of the time and failed to gain properly. Necropsy revealed that the spleen was absent, and the lungs showed a chronic amniotic fluid pneumonia. Death in this case was found to be due to acute bacterial endocarditis with emboli to the blood vessels of the lower third of the left leg, resulting in thrombosis and gangrene.

GARD, Galveston, Texas.

SIMPLIFIED PHOTOELECTRIC PROCEDURES FOR MICRODETERMINATION OF NONPROTEIN NITROGEN, UREA, CREATINE AND CREATININE OF BLOOD. BARNETT SURE and VIOLET WILDER, J. Lab. & Clin. Med. **26**:874 (Feb.) 1941.

A simplified technic with the use of the Evelyn macro-micro photoelectric colorimeter is described. This method can be applied to capillary blood of either small laboratory animals or human beings.

GARD, Galveston, Texas.

THE ISO-AGGLUTININ TITRE OF POOLED SERUM OR PLASMA. R. JAKOBOWICZ and L. M. BRYCE, M. J. Australia **1**:318 (March 15) 1941.

Mixture of samples of serum from blood containing both A and B factors results in reciprocal suppression of the anti-B and anti-A agglutinins to an extent greater than can be accounted for by dilution. This reduction in titer is due to the presence of receptor substances of similar group specificity to the red cell agglutinogens; it is therefore not affected by serum of blood belonging to group O, in which red cell agglutinogens and group-specific receptor substances are absent, and relatively little by that of subgroup A_2, which is characterized by agglutinogens of less avidity for anti-A agglutinins than those of subgroup A_1. The agglutinins in certain specimens of group B serum are not absorbed by group A serum to the extent anticipated. The use of serum (rather than whole blood) for transfusion may increase the likelihood of reactions between introduced agglutinins and the recipient's red cells. A low agglutinin titer is therefore desirable in pooled serum. A practical means of insuring this desideratum is to include in each pooled batch many samples of serum from blood of groups AB, A and B, and to limit the use of serum from group O blood, particularly if it is of high or unknown titer. An alternative method of reducing agglutinin titer by mixture of the serum with suitable samples of boiled saliva is also discussed.

GONCE, Madison, Wis.

HEMORRHAGIC DIATHESIS AND ITS TREATMENT. G. DINKLER, München. med. Wchnschr. **88**:92 (Jan. 24) 1941.

The author tabulates a great many conditions which may cause hemorrhage and discusses the treatment in detail. No mention is made of hemorrhagic diathesis of the newborn or of therapy with vitamin K.

BRAHDY, Mount Vernon, N. Y.

Diseases of Nose, Throat and Ear

CONSERVATIVE TREATMENT OF SINUSITIS IN CHILDREN. ROBERT GEWANTER, Arch. Otolaryng. **32**:728 (Oct.) 1940.

The author stresses the increasing recognition of the prevalence of nasal sinusitis in children. Development of the sinuses, physiology and pathology are discussed. The importance of obtaining an accurate and complete history from the parent in diagnosing is emphasized.

Transillumination and roentgenograms, two valuable aids for diagnosing sinusitis in adults, are not advocated for confirming the clinical diagnosis in children. The Proetz displacement irrigation is outlined; it is advocated because it assists the function of the cilia, helps the epithelium to cleanse and unburden itself and is usable when intranasal instrumentation is practically eliminated.

GREENWOOD, Chicago.

HEMANGIOMA OF THE LARYNX IN INFANTS. O. W. SUEHS and P. A. HERBUT, Arch. Otolaryng. **32**:783 (Oct.) 1940.

A case of infantile hemangioma of the larynx, an uncommon condition and rarely reported in the literature, is presented.

GREENWOOD, Chicago.

POSTOPERATIVE SINUS THROMBOSIS. HANS BRUNNER, Arch. Otolaryng. **33**:509 (April) 1941.

The author discusses latent and postoperative sinus thrombosis as two distinct types, outlining the fundamental pathologic character, symptom complex and prognosis of each and presenting 2 illustrative cases from more than 150 of his own experience.

GREENWOOD, Chicago.

SINUS INFECTIONS: THEIR RELATIONSHIP TO RESPIRATORY DISEASE. FERRIS ARNOLD, California & West. Med. **54**:270 (May) 1941.

Operations on the sinus should rarely be performed on children. Tonsils and adenoids should not be removed during the course of an acute infection; in the presence of chronic or subacute infection, however, they are often the site of residual infection and should then be removed. Infections of the nasal accessory sinuses are important etiologic factors in respiratory disease. It is a mistake to assume that any vaccine or protein injection treatment will cure the sinus infection unless proper drainage has been obtained and foci of infection have been removed.

DAVIS, San Francisco.

CHRONIC NASAL CATARRH IN CHILDREN. AUSTIN FURNISS, Brit. J. Phys. Med. **4**:22 (Feb.) 1941.

The author discusses sinusitis in children. Among other symptoms he mentions a paroxysmal cough, suggestive of whooping cough. He believes that roentgenographic examination constitutes a more delicate diagnostic test than puncture.

In his experience the Proetz method of displacement is especially successful in children. The principle of treatment is to apply repeated negative pressure to the nose and allow iodized oil to percolate into the sinuses. This method is particularly applicable when the sinusitis involves the ethmoid and sphenoid sinuses.

For acute sinusitis the author recommends the use of luminous heat administered directly over the face followed by local and general actinotherapy. He resorts to surgical intervention when adequate drainage cannot be established.

HARTMAN, Cleveland.

Diseases of Lungs, Pleura and Mediastinum

THE ADMINISTRATION OF SULFAPYRIDINE AND ITS CONGENERS IN PNEUMONIAS. JESSE BULLOWA, H. D. RATISH, A. DAVIDSON and C. LEBAIR, New York State J. Med. **40**:1450 (Oct. 1) 1940.

This article gives a general description of the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). It includes a discussion of concentration, excretion, conversion, distribution and clinical application.

AIKMAN, Rochester, N. Y.

THE INFLUENCE OF SULFAPYRIDINE ON THE PNEUMONIAS OF CHILDHOOD: A CLINICAL STUDY OF 85 CASES AT A MUNICIPAL HOSPITAL. SAMUEL L. ELLENBERG and HARRY S. ALTMAN, New York State J. Med. **40**:1457 (Oct. 1) 1940.

The authors report a study of 85 cases of pneumonia treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Six deaths occurred, giving a mortality rate of 7 per cent. Sulfapyridine was found to be of great therapeutic value, but it had little effect in preventing complications of pneumonia.

AIKMAN, Rochester, N. Y.

INFLUENCE OF SULFATHIAZOLE THERAPY ON PLASMA LIPIDS IN PNEUMONIA. ALBERT V. STOESSER, Proc. Soc. Exper. Biol. & Med. **46**:83 (Jan.) 1941.

Study of the serum lipids of 6 children of 6 to 13 years suffering from pneumonia was made before, during and after the administration of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole). The low values for total cholesterol, cholesterol ester, total fatty acids and phospholipid fatty acids rapidly rose to normal with clinical improvement. The results obtained corresponded more closely to those observed following specific serum administration than to those following the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). The author believes that the changes in the lipids may follow the development of immune bodies.

HANSEN, Minneapolis.

PROLIFERATIVE MURAL BRONCHIOLITIS. ST. ENGEL and G. H. NEWNS, Arch. Dis. Childhood **15**:219 (Dec.) 1940.

Five cases of mural bronchiolitis are reported with detailed postmortem findings. The gross change is an enormous thickening of the bronchiolar wall and collapse of the lung tissue. This, and not peribronchiolar infiltration, is responsible for the macroscopic picture of disseminated bronchopneumonia. The center of the lesion is situated in the medium bronchioles. Larger bronchioles, especially when furnished with a definite basal membrane, and bronchi are much less affected. This applies to the infiltration of the wall as well as to the engorgement of the vessels. The proliferative part of the lesion affects predominantly the basal cells and the epithelium. True pneumonia may develop as a consequence of mural bronchiolitis, but this is a secondary process. Many facts point to the possibility of virus infection as a cause of proliferative mural bronchiolitis. The clinical picture in the cases cited was indefinite. The possibility that proliferative mural bronchiolitis might be a disease sui generis is put forward for discussion.

KELLY. Milwaukee.

TREATMENT OF PNEUMONIAS IN CHILDREN WITH SULFAPYRIDINE, ORALLY AND INTRAMUSCULARLY. L. K. TSANG and MARY E. MCCRACKEN, Chinese M. J. **58**:629 (Dec.) 1940.

The authors have tabulated 378 cases of pneumonia treated with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). In these cases the mortality percentage rate was about 1, contrasting with figures in textbooks of 3 to 5 for lobar

pneumonia, 10 to 20 for primary bronchopneumonia and 50 to 80 for secondary bronchopneumonia in institutions. They point out the early recovery of the child who receives such treatment as an indication of the therapeutic value of sulfapyridine in addition to the lowering of the mortality.

The literature indicates that sulfapyridine is at this time the best therapeutic agent for children; it is equally effective orally and intramuscularly. In the muscle a suspension-solution with 0.8 per cent sodium hydroxide may be used. Relatively larger doses are needed for children than for adults in order to get the best results. After this parenteral use of 1.5 to 2.0 Gm. for children under 30 pounds (13.5 Kg.) and of 3.0 Gm. for those over 30 pounds, an effective blood level, of over 4 mg., may be maintained for seventy-two hours.

NEFF, Kansas City, Mo.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

NONSPECIFIC MESENTERIC LYMPHADENITIS: REPORT OF FIFTY-EIGHT CASES. IRWIN PHILIP SOBEL and DEWITT STETTEN, J. Pediat. **17**:305 (Sept.) 1940.

The authors report 58 proved cases of nonspecific lymphadenitis. All but 5 of the patients were under 20 years of age. In 43 per cent of the cases a biopsy of one or more lymph nodes was performed. Probatory excision of a mesenteric node is devoid of danger if carefully performed. In 38 per cent of the cases an excess of free peritoneal fluid was found at operation. Definite adhesions of the appendix were present in 40 per cent of the cases. The authors do not subscribe to any of the current theories concerning mesenteric lymphadenitis but feel that there is some relation to disease of the appendix. It is suggested that if at operation for acute appendicitis in a child or adolescent the condition of the appendix does not explain the clinical picture, a careful exploration for inflamed mesenteric nodes should be made, especially at the root of the mesentery. A definite diagnosis of mesenteric lymphadenitis must at present be reserved for the operating table. Sobel and Stetten advise operation not merely for diagnosis but because appendectomy, in some way still not very well explained, favorably affects the course of the disease.

RAUH, Cincinnati.

ACUTE HEPATITIS, JAUNDICE AND ABNORMAL BLEEDING AS COMPLICATIONS OF ACUTE APPENDICITIS WITH PERFORATION. F. A. SIMEONE and JOHN D. STEWART, New England J. Med. **223**:632 (Oct. 17) 1940.

Fatalities following operations for acute appendicitis with perforation and peritonitis are usually the result of spreading peritoneal sepsis and its complications. In this report the authors discuss 2 cases of intraperitoneal sepsis in children, complicated by hepatitis and terminal bleeding.

The first patient, a 17 year old boy, died thirteen days after operation, and the second, a 13 year old girl, died fifteen days after operation. In the 2 cases described, the abnormal bleeding was probably due to a disorder in the absorption or utilization of vitamin K. The disturbed liver functions attending the hepatitis may have interfered with the normal reaction whereby vitamin K effects the liberation or activation of prothrombin in the liver.

In these cases, vitamin K therapy should be actively supplemented by transfusion to combat the low plasma prothrombin concentration.

GENGENBACH, Denver.

CONGENITAL DIAPHRAGMATIC HERNIA. WILLIAM E. LADD and ROBERT E. GROSS, New England J. Med. **223**:917 (Dec. 5) 1940.

Sixteen patients with congenital diaphragmatic hernia have been operated on at the Children's Hospital since 1930. Of the 9 patients who recovered, 7 were less than 1 year of age. The youngest patient was operated on when 40 hours

old. One of the 7 deaths occurred five days after a phrenicectomy, before the herniorrhaphy was attempted; another occurred four days after operation, probably from pneumonia. The remaining 5 deaths were probably due to one or a combination of the following factors: failure to provide proper fluid balance, lack of positive pressure anesthesia or too tight closure of the abdominal wall. The authors emphasize the importance of postoperative treatment.

The authors' summary is as follows:

"The time to make the diagnosis of congenital diaphragmatic hernia is immediately after the baby is born. The time to attempt cure is within the first few days after birth. . . . The policy of delaying operation until the infant is older is a hazardous one, and has been responsible for many deaths in the past.

"One of the greatest problems of operating on these patients in early infancy has been that of finding sufficient room in the underdeveloped peritoneal cavity to receive the abdominal viscera. This problem has now been solved by the procedure . . . of closing only the abdominal skin, allowing the abdominal wall to stretch and then suturing the peritoneum and the rectus muscles at a second operation five or six days later. . . ."

GENGENBACH, Denver.

HISTOLOGIC CHANGES IN THE ESOPHAGUS RESULTING FROM INGESTION OF CAUSTICS. V. SANGIOVANNI, Arch. ital. di otol. **51**:1 (Jan.) 1940.

After applying potassium hydroxide, phenol, mercury bichloride, silver nitrate and sulfuric acid with a swab to the lining of the esophagus in 14 dogs, Sangiovanni studied the effect on the animals of these cauterizing agents. Most of the dogs died from the lesions within a few days; 1 was kept alive for four months by gastrostomy, and another, with severe lesions of the esophagus and without gastrostomy, lived for five months; 3, with insignificant lesions, were killed three months after the tests. Autopsy and microscopic examination of the tissues were carried out in all cases. The gravest lesions encountered were those from mercury bichloride. These occurred not so often in the esophagus as in the kidneys and killed the dogs in from ten hours to three days; in each case an intense edema of the cauterized regions was found, and noteworthy were the deposits of calcium salts in the renal tissues, due to the decalcifying action of the mercury on the bones.

The anatomic lesions encountered soon after the cauterization varied in intensity with the caustic employed. Sometimes only the mucosa was involved, but usually both the mucosa and the submucosa were compromised. Phenol produced less profound local lesions; grave destructive lesions, leading even to the destruction of neighboring organs, were produced by potassium hydroxide; the lesions produced by silver nitrate were superficial, but the author was interested to observe deposits of silver in the renal tissues; the animal which was submitted to the action of sulfuric acid (50 per cent solution) evinced no symptoms, although the cauterization was repeated after one month. This dog was killed after three months, and examination revealed no lesions except a slight thinning of the epithelial layer.

The zones showing the more intense lesions were those corresponding to physiologic constrictions. Of the 4 dogs on which phenol was used, death occurred in the first three days and was caused by toxic nephritis and bronchopneumonia; the second also died in three days, from a general toxic state, hemorrhagic nephritis and bronchopneumonia; the third dog lived seventeen days, and the fourth was killed after four months, and in both reparative phenomena and consecutive stenosis had followed the destructive process. The evolution of the lesions from potassium hydroxide was very severe by reason of the profound alterations characteristic of the action of this substance; one dog died in six days with tracheoesophageal fistula; the second died in twenty-five days, from inanition because of a cicatricial stenosis of the esophagus, and the third died after five months from inanition due to cicatricial stenosis of the esophagus and periesophagitis. To be noted also in the survivors was the appearance of dilatation of the esophagus above the stricture

The results of the experiments agree with the observations made on human beings subjected to the ingestion of caustics, except that in the dog cauterized with sulfuric acid no grave lesions were found. This fact may be dependent on local factors or on the use of an unsuitable concentration. The stenoses were analogous to those observed in man as to their location, their histologic aspect and the occurrence of dilatation above the stricture. Noteworthy was the occurrence of midgastric stenosis due to perigastritis in a dog which was cauterized with phenol. Sometimes caustics may produce slight lesions of the esophagus and much graver lesions in the stomach.

Detailed protocols of the cases are furnished.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

Nervous Diseases

NEUROLOGIC SYNDROMES ACCOMPANYING DEVELOPMENTAL ANOMALIES OF OCCIPITAL BONE, ATLAS AND AXIS. CARL F. LIST, Arch. Neurol. & Psychiat. **45**: 577 (April) 1941.

This excellent article gives a detailed account of the embryologic defects of the base of the skull, axis and atlas causing pathologic neurologic syndromes. The symptoms and treatment are also discussed. BEVERLY, Chicago.

VITAMIN THERAPY OF DISEASES OF THE NEUROMUSCULAR APPARATUS. A. M. DOYLE and H. H. MERRITT, Arch. Neurol. & Psychiat. **45**:672 (April) 1941.

From observation of 12 cases the authors were unable to confirm reports that vitamin therapy results in improvement of patients having amyotrophic lateral sclerosis or other forms of muscular atrophy. BEVERLY, Chicago.

NEURAL MATURATION AS EXEMPLIFIED IN THE CHANGING REACTIONS OF THE INFANT TO PIN PRICK. MYRTLE B. MCGRAW, Child Development **12**:31 (March) 1941.

In an attempt to appraise maturation or reorganization of sensorimotor mechanisms in the infant, 75 children were stimulated by pinprick at repeated intervals from birth to 4 years. In addition longitudinal studies were made on 4 infants during the first eighteen or twenty-four months of life. Changing responses in this situation were analyzed into (*a*) sensorimotor aspects of the behavior, based on response to the actual application of the pinprick, and (*b*) cognitive and conative aspects, based on response to the sight of the pin and to the situation in general. Four major developmental phases were found in each category. These phases are interpreted in terms of subcortical and cortical function. The reactions of the newborn are considered to be subcortical or thalamic; general localization of the stimulated area is considered the first distinct evidence of cortical participation in the function. The sensorimotor aspects of the behavior were found to develop earlier than the cognitive and conative aspects; general localization is established before any association is made between the pin and the subsequent disagreeable stimulation, and specific localization is well established before the child achieves integration of the various centers which permit adequate appraisal of the whole situation. DAMMANN, Washington.

STAPHYLOCOCCUS AUREUS MENINGITIS SUCCESSFULLY TREATED WITH SULFATHIAZOLE. FREDERICK W. DIETEL and ALBERT D. KAISER, J. A. M. A. **115**: 601 (Aug. 24) 1940.

Injury to the residuum of a furuncle probably introduced Staphylococcus aureus infection into the meninges of the 20 month old child whose case the authors report.

Administration of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in doses of 40 grains a day by gavage, daily spinal punctures, irrigation with saline solution and blood transfusions were successfully carried out, and the child made a complete, uncomplicated recovery. HEERSMA, Kalamazoo, Mich.

CEREBELLAR AGENESIS. H. S. RUBINSTEIN and WALTER FREEMAN, J. Nerv. & Ment. Dis. **92**:489 (Oct.) 1940.

Rubinstein and Freeman report the case of a Negro who had always been subnormal mentally but had been self supporting since adolescence, and who had showed no evidence of motor dysfunction until the age of 69. At that time he began to fall occasionally. At 72 he was stooped, showed marked incoordination and exhibited sluggish pupils, slurred speech, intention tremor and "athetoid" movements. There was memory defect with vague delusions. Death occurred at 74, of tuberculosis. Necropsy revealed arteriosclerosis, softenings in the left parietal region and numerous developmental anomalies. On the right side there were defects in the superior and inferior colliculi, the trigeminal mesencephalic system, the lateral lemniscus, the medial geniculate body and the vestibular nuclei. Of the cerebellum, only two fairly well developed flocculi were present, which received fibers from the superior vestibular nuclei. There appeared a trace of vermis to the left of the midline and three simple folia of the lateral lobe on the right. Except for some microgyria, the microscopic appearance was normal in the existing portions of the cerebellar cortex. Masses of gray glial tissue were situated at the sides of the fourth ventricle. The roof nuclei were not present, and only a small part of the left nucleus emboliformis was noted. The restiform bodies were thin; the pons was very small, with only a few cells in its nuclei, and the brachium conjunctivum was poorly myelinated on both sides. The red nuclei were small, especially on the left. The inferior olive was of simple formation, with the medial accessory olive poor in cells and the dorsal accessory olive absent. The central tegmental tract was scarcely identifiable, and only thin bundles of myelinated fibers encircled the olive and formed the olivothalamic tract.

Rubenstein and Freeman point out that, except for bilateral cerebellar agenesis, the important neural deficiencies were largely unilateral. Two processes seemed responsible: defective closure of the neural tube on the right and bilateral cerebellar aplasia. The portions of the cerebellum present were phylogenetically the oldest. These simple cerebellar structures sufficed to carry out cerebellar function during most of the patient's life, not because of any compensating mechanism, but probably because the patient functioned "on a lower psychosomatic, social, economic and intellectual level." MACKAY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

MANAGEMENT OF CEREBRAL GLIOMAS. G. PHILLIPS, M. J. Australia **2**:301 (Oct. 5) 1940.

Phillips reports 2 deaths in hospitals in a series of 35 consecutive cases of cerebral or cerebellar tumors removed surgically. One death occurred eight weeks after operation as a result of an accident, while the other occurred fourteen days after operation as the result of intracranial hemorrhage. Twenty-eight of the 35 operations were performed in the presence of a large space-occupying lesion in the skull, associated in each instance with a considerable increase of intracranial pressure; 1 patient died as the result of late wound infection. The results substantiate the claim that with adequate management cerebral tumors may be exposed and removed with a relatively low surgical mortality rate. Operation with local anesthesia makes this possible. The patient's ability to complain of pain, cold and discomfort and the opportunity to provide adequate fluid by mouth during prolonged surgical procedures are constant guardians against cerebral shock. Except with children, the author rarely uses general anesthesia. Twenty- two of the intracranial tumors were gliomas. The whole tumor was removed in 10 cases and the greater part of the tumor in 8; in 4 cases, for various reasons, no attempt was made to remove the tumor, which after exposure was treated with high

voltage roentgen radiation. The author believes that, irrespective of the skill of the surgeon, operations for cerebral glioma will frequently be succeeded by a fatality if these tumors are considered as a single group and submitted to indiscriminate surgical procedure. Particularly is this so since nearly 40 per cent are glioblastomas. A major responsibility for the surgeon is to equip himself with information concerning the frequency, location and full life history of cerebral gliomas. The capacity for diagnosing cerebral gliomas preoperatively is almost the *sine qua non* of continued success. The pertinent facts are summarized. The percentages for the different types of gliomas are: glioblastomas 40, astrocytomas 40, medulloblastomas 12, oligodendrogliomas 2, ependymomas 2 and all the rare types 4. The average postoperative period of survival for the respective tumors is twelve months, six to ten years, two to four years, more than six years, and six to ten years; for the rare types the survival time is variable. The average age at which glioblastomas occur is between 40 and 60; for astrocytomas of the cerebrum it is 30 and for those of the cerebellum 13; the average age for medulloblastomas is 10 and for oligodendrogliomas 30; the ependymomas and the rare types occur at various ages. J. A. M. A.

THE AYALA INDEX OF THE CEREBROSPINAL FLUID. I. M. ALLEN, New Zealand M. J. **40**:43 (Feb.) 1941.

The Ayala index (the estimated ratio of the fall of pressure of the cerebrospinal fluid to the fall of its volume) is only of limited value in the light of facts collected from repeated neurologic examinations. Estimation of the Ayala ratio can be of some value empirically in certain cases, although difficulties involved in estimation and interpretation render the test impractical for the most part.

WEIGAND, Indianapolis, Ind.

TRUE CONGENITAL FACIAL PARALYSIS. ATILIO VIALE DEL CARRIL, Rev. argent. de oto-rino-laring. **9**:85 (March-April) 1940.

After a review of the literature del Carril presents a case of true congenital facial paralysis. Assuming that the etiologic factors in this patient could not be altered by any type of treatment, he employed symptomatic measures to correct the deformity.

He noted that on account of atrophy of the facial muscles there was a deviation of the lower jaw to the healthy side and that, in consequence, there was a definite malocclusion of the teeth. He made an orthodontic prosthesis, which corrected this malocclusion. In addition, the patient was instructed to take daily muscular exercises to strengthen the facial muscles.

After a year and a half of observation, he found that the general appearance of the patient was markedly improved, and his photographs show the patient "before and after" treatment. PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Psychology and Psychiatry

SOME PHYSIOLOGICAL CHANGES DURING FRUSTRATION. HUDSON JOST, Child Development **12**:9 (March) 1941.

A total of fifty-two physiologic measures were taken during several experimental situations in 18 emotionally unstable and 20 very stable children. The physiologic measures were those of respiration, galvanic skin resistance, pulse rate, muscle tension and brain waves. The various experimental situations consisted of rest, attention, learning, frustration, recall and sensory stimulation.

The ten measures which were most significant in the differentiation between the stable and unstable groups were initial galvanic skin resistance, change of level of resistance during learning, changes of resistance during frustration, equa-

tion of galvanic responses at attention and sensory stimulation, hand tremor before and after frustration, change in blood pressure at sensory stimulation, dominance of alpha rhythm in the electroencephalogram, standard deviation of the amplitudes of respiratory movements and change in heart rate after frustration. The experimental group showed an exaggerated physiologic reaction pattern as well as a slower return to the prestimulus level of physiologic activity. The variance of the measures of the unadjusted persons from the mean measures of the adjusted group gave a good indication of the degree of emotional disturbance. These measures correlated 0.79 with the ratings of these children regarding their emotional reactivity. The psychotic and well adjusted persons presented the most stable physiologic patterns; whereas the prepsychotic and neurotic persons presented the most unstable patterns. Unstable persons reacted more violently to a frustration situation than did the stable persons, as measured by their physiologic reactions.

DAMMANN, Washington.

A STUDY OF THE INTELLIGENCE OF ITALIAN AND POLISH SCHOOL CHILDREN FROM DETERIORATED AND NONDETERIORATED AREAS OF CHICAGO AS MEASURED BY THE CHICAGO NONVERBAL EXAMINATION. ANDREW W. BROWN and CAROL B. COTTON, Child Development **12**:21 (March) 1941.

The purpose of this study was twofold: first, to compare the intelligence test responses of Italian and Polish children living in deteriorated areas (areas of low socioeconomic status and high rates of delinquency) with those of children of the same nationalities living in nondeteriorated areas; second, to determine the degree to which the intelligence of children of Polish and Italian parentage approximates that of the general population when the language factor is held constant.

In 1936, school children in grades 4 to 8 in deteriorated areas with a highly concentrated Italian and Polish population were given verbal and nonverbal tests. The same tests were given to Italian and Polish children in nondeteriorated areas. The two groups in the two areas are compared with regard to age, sex and length of parents' residence in America, as well as with regard to socioeconomic status. In 1940 those children who were still in the elementary school were reexamined. The results of this follow-up study will be reported.

Results indicate (1) that Italian children (both boys and girls) in the deteriorated areas make higher scores than those in the nondeteriorated areas, but that the reverse is true of Polish children, (2) that for both national groups and for both sexes there is a fairly consistent drop in intelligence quotient with age in both areas; (3) that, in general, both national groups in both areas make lower scores than the children of the general population, but that the difference between the national groups and the general population on nonverbal tests is not so great as it is on verbal tests.

DAMMANN, Washington.

PARENTS' REPORTS OF UNDESIRABLE BEHAVIOR IN CHILDREN. ALMA LONG, Child Development **12**:43 (March) 1941.

The data collected relate to the presence of behavior problems at various age levels, in typical family constellations, with differing socioeconomic environment, age and education of parents, and also in connection with methods of discipline used by parents.

An anonymous questionnaire which urged candid replies from parents was used. Fifty-seven items of undesirable behavior and twenty child-training methods were included for checking. Other items and explanatory comment were to be added if parents so desired.

The frequencies indicate significant trends in undesirable behavior related to the age of the child. Tetrachoric coefficients of correlation between behavior items indicate generally low interrelationships, with an average correlation of 0.12 in a range of -0.45 to $+0.65$. There were indications of trace relationships which extended into three or more types of behavior. Lack of adequate information

concerning principles of behavior development appeared to characterize a high percentage of the parents in the group, even though many of them had graduated from high school and college and were interested enough in the study of child behavior to cooperate in this study. DAMMANN, Washington.

PHYSICAL COMPLAINTS WITHOUT ORGANIC BASIS. MARY I. PRESTON, J. Pediat. **17**:279 (Sept.) 1940.

One hundred cases of physical complaints without organic basis in a group of children aged 4 to 20 years were studied. Twenty-one of these children were intelligent pupils who, through no fault of their own, had not been taught to read. In over 95 per cent of the cases complaints were found to serve a definite and important need in the children's lives, that of ameliorating intolerable situations or of solving intricate problems beyond their power. Continuance of these complaints had impaired the physical health of four fifths of these children. Only 6 per cent escaped symptoms of mental ill health in varying degrees as the whole organism became involved. In attacking these cases a study of the child's emotional life and relationship in home, social and school circles was found essential. The factors found most helpful as clues to the cause of the physical complaint were as follows: frightening experiences of the patients; school problems, especially in intelligent patients; lack of parental love; social failure; anxiety over the meaning of death; threatened banishment; sex and other psychic trauma; contact with hypochondriacs and oversolicitude in family members, and exploitation by overambitious parents and teachers. Symptoms confirmatory of serious trouble were excessive daydreaming, crying and going to pieces easily, being worried much of the time, being filled with fears, playing alone and, in the intelligent child, lessened ability to learn. The outcome of treatment by simple, direct and common sense methods was highly successful, with loss of complaints and restoration to health in 85 per cent of the children. RAUH, Cincinnati.

PHYSICAL DEFECTS AND JUVENILE DELINQUENCY. EUGENE W. WALLACE, New York State J. Med. **40**:1586 (Nov. 1) 1940.

A study was made of 200 juvenile delinquents referred to the author at the Children's Hospital in Buffalo by the Children's Court for physical examination. There were 166 boys and 34 girls, ranging from 9 to 16 years of age. Nearly 65 per cent of the boys were above normal height standards; 33 per cent of the boys and 11.7 per cent of the girls were more than 10 pounds above the average in weight. About 85 per cent of the group could be classified as well developed and nourished. However, only 3 per cent were found free of physical defects. Among other defects, errors in refraction were found in 28 to 34 per cent and dental caries was found in 72 per cent. Delinquents are more mature physically than average children; this suggests that children who present advanced maturity need extra supervision. AIKMAN, Rochester, N. Y.

PEDIATRIC RESPONSIBILITIES IN MENTAL HYGIENE. J. S. HUNT, South. M. J. **34**:72 (Jan.) 1941.

The author reports that of the three components of growth and development in human beings—the physical, the intellectual and the emotional—only the emotional phase has shown unsatisfactory progress up to the present.

The average age at which the private pediatrician is consulted on abnormal behavior is 70 months (nearly 6 years); but forced feeding, the earliest and most frequently demonstrable cause of abnormal behavior, may begin at 10 to 12 months. The pediatrician must therefore make himself alert to minor problems tending to create abnormal behavior, lest he fail in the field of preventive medicine, his most important field.

A child specialist has the right to talk about child management as a part of mental hygiene, for abnormal behavior is the seventh most commonly encountered

condition which he is called on to treat. He is thus faced with the duty, rather than the right, of increasing his knowledge of mental hygiene, a field into which he is forced whether he wishes to enter it or not. SCHLUTZ, Chicago.

Diseases of the Genitourinary Tract

MENSTRUAL DISORDERS DURING THE ADOLESCENT PERIOD. RALPH E. CAMPBELL, Illinois M. J. **79**:454 (June) 1941.

The author summarizes this article as follows:

"1. A thorough history, a complete physical examination, and extended laboratory aids are necessary in diagnosing and treating the menstrual dysfunctions of adolescence.

"2. Menstrual irregularities in the adolescent period are manifestly associated with and related to conditions arising in both the pre-pubertal and pubertal periods.

"3. Primary amenorrhea in a healthy girl with good pre-pubertal development may delay active treatment. However, primary amenorrhea with faulty pre-pubertal development may finally indicate active treatment. . . .

"4. Functional bleeding during the adolescent period usually corrects itself and only excessive blood loss should indicate active treatment. . . . The gonadotropic substances are certainly indicated as a method of treatment in this complication because they initiate ovulation. . . .

"5. Dysmenorrhea may be treated from the endocrine standpoint, but other factors must not be overlooked.

"6. The thyroid gland extracts should not be forgotten in menstrual irregularities, even though the treatment may be empirical. The thyroid dosage should be guarded and controlled in part by basal metabolic rate determinations.

"7. The anterior pituitary-like substances should be used with distinct caution because of their tendency to produce follicular atresia.

"8. Caution should be exercised in the use of testosterone propionate because of the tendency to hirsutism and masculinization." BARBOUR, Peoria, Ill.

VULVAR FUSION: ITS UROGYNECOLOGIC INTEREST. MEREDITH F. CAMPBELL, J. A. M. A. **115**:513 (Aug. 17) 1940.

Campbell discusses vulvar fusion and his experience with 9 cases. The patients were referred after diagnosis of external genital anomalies and pyuria. The fusion was relieved quite simply by means of a probe, and the labia were separated to prevent recurrence. The obstruction at the urethral orifice had produced the urinary changes. HEERSMA, Kalamazoo, Mich.

CARCINOMA OF THE BREAST IN A TEN-YEAR-OLD GIRL. JOHN B. SEARS and MONROE J. SCHLESINGER, New England J. Med. **223**:760 (Nov. 7) 1940.

In the last three decades only 2 well authenticated cases of cancer of the breast occurring before puberty have been reported; 1 patient was a girl of 11 years and the other a girl of 12.

In this article the authors report the case of a 10 year old white American-Irish schoolgirl, who came to the outpatient department of a hospital because of a lump in the right breast. Six years previously her mother had noted the lump. There was no history of pain or tenderness. Physical examination revealed a nodule 3 by 2.5 by 2.5 cm. under the right nipple. It was hard, irregular, sharply circumscribed, nontender and adherent to the overlying nipple, which was flattened. The mass was freely movable posteriorly. There were no lymph nodes in the axilla or supraclavicular region. Roentgen examination of the tumor showed no evidence of calcification; that of the long bones, skull and chest showed no evidence

of metastasis. The breast tumor and pectoral fascia were excised. Eight days after the operation the patient was discharged to the tumor clinic for follow-up. At the end of a year there was no evidence of recurrence.

The pathologist's diagnosis was adenocarcinoma of the breast, grade II.

GENGENBACH, Denver.

A CRITICAL REVIEW OF CASES OF SO-CALLED REFLEX ANURIA, WITH THE REPORT OF A CASE. P. L. HIPSLEY, M. J. Australia **2**:602 (Dec. 7) 1940.

Study of the literature and of 4 cases of his own leads Hipsley to the conclusion that reflex anuria (sudden cessation of kidney function usually following some surgical procedure) is almost certainly due to calculi lodged in both ureters. The symptoms recorded in all cases are similar to those commonly seen in renal colic due to stone—severe pain in the loins, vomiting, hematuria, absence of fever and absence of evidence of renal damage either before or after the attacks. In most of the reported cases the patients have been children, and it is known that renal calculi are not uncommon in children. The only reason that anuria is not noted more frequently after the administration of sulfapyridine is that the chances of a simultaneous bilateral ureteral block must necessarily be small. The increasing use of sulfapyridine, however, may be expected to be followed by a greater number of cases of bilateral ureteral obstruction than have been so far reported. Most of the cases of anuria reported in the *Medical Journal of Australia* have followed appendectomy, and in most of these cases one cannot be sure that the colic prompting the operation was not renal rather than appendical. In the treatment of so-called surgical anuria, decapsulation alone is quite useless and ureteral catheterization, although it may effect a cure, has failed in most cases in which it has been attempted. The only certain method of draining the pelvis is by pyelostomy or nephrostomy. Intravenous injections of dextrose, saline or sodium sulfate solution may occasionally be successful, since they may raise the pressure within the renal pelvis enough to displace the calculi. GONCE, Madison, Wis.

ACUTE NEPHRITIS IN CHILDHOOD. S. L. LUDBROOK, New Zealand M. J. **40**:13 (Feb.) 1941.

The author presents a detailed analysis of the causation, symptoms, complications, treatment and immediate prognosis in 105 cases of acute nephritis in children up to the age of 15 years. The close relationship between acute nephritis and infections due to the hemolytic streptococcus is confirmed. The causes of cerebral complications, particularly the convulsive phenomena, are discussed in relation to observations of blood pressure and the total nonprotein nitrogen of the blood. In treatment a normal fluid intake was maintained in all patients, and no apparent ill effects were caused by this regimen. In no case did there appear to be any increase of edema as a result of free administration of fluids.

Sixty of the 105 patients were followed for an average period of six years after the attack. Of these, 97 per cent appear to be cured according to the standards laid down. The ultimate prognosis in acute nephritis of childhood is good.

WEIGAND, Indianapolis, Ind.

ENDOCRINE THERAPY OF CRYPTORCHIDISM. A. CAPPELLO, Med. ital. **21**:155 (April) 1940.

The author treated several patients with cryptorchidism with anterior pituitary preparations, with gonadotropin and with testosterone proprionate. He concludes that gonadotropin gave the best results. Some patients must be treated surgically—namely, those with torsion of the testicle and those in whom the cryptorchidism is due to mechanical obstruction.

MARTOCCIO, Utica, N. Y.

AMENORRHEA DURING PUBERTY IN WORK CAMPS. H. ALBRECHT, München. med. Wchnschr. **88**:138 (Jan. 31) 1941.

Albrecht answers a question concerning the increasing incidence of amenorrhea in young girls who are employed in work camps. Any change in environment, mode of life or climate may affect the labile edocrine system during puberty. Because more young women are working, there will be an increase in menstrual disturbances during puberty. In most instances the condition is transient and not associated with ill health. However, if the amenorrhea lasts longer than six months or there is an associated loss of weight, fatigue or nervousness, the patient should be released and sent home. Usually this results in the reestablishment of menstruation. For treatment sitz baths and iron therapy are suggested. If after another four months there is no improvement, endocrine therapy is indicated. However, according to the regulations this is too expensive for the insurance doctor to undertake.

BRAHDY, Mount Vernon, N. Y.

Diseases of the Ductless Glands; Endocrinology

THE PSYCHICAL ACTIVITY OF MALE AND FEMALE SEX HORMONES OF HORSE URINE. PAUL ENGEL, Endocrinology **28**:849 (May) 1941.

Many investigations have indicated an antagonism between androgen and estrogen. In this experiment, however, it was found that the same extract of male horse urine (which contains both estrone and testosterone) was able to restore normal activity to castrated male guinea pigs and also to produce all the changes in the female characteristic of the presence of estrone.

The conclusion is that the presence of one of the substances does not inhibit the activity of the other.

JACOBSEN, Buffalo.

THYROGLOSSAL CYSTS AND SINUSES (A STUDY AND REPORT OF 198 CASES). ROBERT E. GROSS and MARION L. CONNERLEY, New England J. Med. **223**:616 (Oct. 17), 1940.

The authors review and report the findings from 198 cases of midline cervical cysts and sinuses arising from the thyroglossal duct. All these cases were observed at the Boston Children's Hospital.

In approximately 85 per cent of the patients the lesions were cysts, and in about 15 per cent they were sinuses. Cysts range in size from that of a pea to that of a golf ball. An average cyst is 1 to 2 cm. in diameter.

In 3 cases there was a small swelling at the base of the tongue which proved to be a thyroglossal cyst. In 29 per cent of the cases the lesions were noted at birth, and in 76 per cent the symptoms began before the sixth year.

Thyroglossal duct sinuses and cysts are slightly commoner in girls than in boys, the respective proportions of the two in the present series being 56 and 44 per cent.

Branchiogenic cysts should rarely give difficulty in differentiation. These have a more lateral position, tending to occur along the anterior border of either sternomastoid muscle. Of the 198 patients, 110 had been surgically treated, while 88 had not been operated on.

Operative treatment should always include resection of the central part of the hyoid bone and also removal of a block of tissue upward as far as the base of the tongue.

GENGENBACH, Denver.

REPORT ON MEDICAL PROGRESS: THE TREATMENT OF JUVENILE DIABETES MELLITUS. ALLAN M. BUTLER, New England J. Med. **223**:900 (Nov. 28) 1940.

Butler discusses fully the relative merits of two methods of treatment to combat evidences of hyperglycemia occurring at various times during the twenty-four hour period: (1) the use of a low carbohydrate intake combined with the administration

of protamine insulin alone; and (2) the use of a higher carbohydrate intake with the combined administration of protamine insulin and plain insulin. The author prefers the latter method of procedure and from his extensive experience gives in detail what he terms "rules of thumb" to meet all exigencies occurring in the course of treatment.

GENGENBACH, Denver.

REDUCTIONS IN BLOOD PRESSURES OF RENAL HYPERTENSIVE DOGS BY HOG RENIN. G. E. WAKERLIN and C. A. JOHNSON, Proc. Soc. Exper. Biol. & Med. **46**:104 (Jan.) 1941.

Four dogs rendered hypertensive by means of renal ischemia were given hog renin, with decided decrease in the level of the blood pressure. After the administration of hog renin was discontinued, hypertension again appeared. Heating hog renin inhibited its antihypertensive effect. Dog renin was ineffective in reducing the blood pressure of these animals with renal ischemia. The mechanism of the reduction in blood pressure is not known. It is possible that an immune (antihormone?) response to heterologous hog renin may be involved.

HANSEN, Minneapolis.

ORAL ANTERIOR PITUITARY EXTRACT (COLLIP) IN DIABETES. R. D. LAWRENCE and F. G. YOUNG, Lancet **2**:709 (Dec. 7) 1940.

In experiments with human diabetic patients and with dogs made permanently diabetic by the administration of anterior pituitary extract for a short period, no evidence was obtained to support Collip's claim that the oral administration of the "primary alcoholic extract of pituitary tissue" exerts a profound "antidiabetogenic effect."

LANGMANN, New York.

Diseases of Muscles, Bones, Joints and Lymph Glands

MUSCULAR DYSTROPHIES OF EARLY CHILDHOOD: A CASE OF FIORE'S FETAL DYSTROPHY. S. FOLENA, Riv. di clin. pediat. **38**:641 (Nov.) 1940.

A case report is given of a child of 12 months with muscular dystrophy, probably congenital. The child died of bronchopneumonia, and extensive postmortem study was made. The condition fell into the category described by Fiore (AM. J. DIS. CHILD. **28**:773 [Dec.] 1924) as fetal dystrophy of the myopathic type with segmental distribution. In the malpighian corpuscles of the spleen there was marked lipid deposit.

HIGGINS, Boston.

CYSTIC LYMPHANGIOMA OF THE NECK CURED BY MEANS OF SUBCUTANEOUS ANASTOMOSIS. A. CABITZA, Riv. di clin. pediat. **38**:681 (Nov.) 1940.

A child of 6 months had a swelling in the left side of the neck about the size of a turkey's egg. This multilocular lymphangioma was operated on with the area under local anesthesia, and the cavity was brought to the surface and sutured to the skin (marsupialization). The end result of the operation was excellent.

HIGGINS, Boston.

GIRDLE-SHAPED DEGENERATION OF THE CORNEA AND ARTHRITIS IN CHILDREN. W. P. C. ZEEMAN, Nederl. tijdschr. v. geneesk. **84**:134 (Jan. 13) 1940.

The small number of cases in which girdle-shaped opacity of the cornea and remnants of iritis in young children are combined with arthritis is increased by the 5 cases described in this clinical report. Only some of the patients were suffering from Still's disease.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Eye

OPHTHALMOMYIASIS INTERNA ANTERIOR. C. S. O'BRIEN and J. H. ALLEN, Am. J. Ophth. **22**:996 (Sept.) 1939.

O'Brien and Allen report the case of a boy who ran a nail into his foot. Ten days later the right eye became red, congested and painful; the lens was found to be subluxated and the tension was 65 mm. of mercury (Gradle-Schiøtz). Biomicroscopic study revealed a gray, translucent, cigar-shaped object, 0.5 mm. in its greatest diameter and 2.5 mm. long, in the anterior chamber. A diagnosis of invasion by a larva was confirmed on removal. The larva proved to be one of Hypoderma. The eye recovered.

W. S. REESE. [ARCH. OPHTH.]

HUMAN CYCLOPIA WITH ASSOCIATED OCULAR ANOMALIES. I. E. WILBER, Am. J. Ophth. **22**:1120 (Oct.) 1939.

Wilber reports a case of cyclopia in an 8 month premature girl who lived for one-half hour after birth. The mother was a normal primipara. The gross and microscopic observations are enumerated, and an interpretation is given from a morphologic and chronologic standpoint, followed by a discussion of the cause of cyclopia. The following summary is given:

"A case of cyclopia, type synophthalmia bilentica, with concurrent ocular anomalies has been described and its embryological development delineated. Modern theories of the teratogenesis of cyclopia have been discussed."

W. S. REESE. [ARCH. OPHTH.]

A CASE OF RHINOSPORIDIUM OF THE CONJUNCTIVA. W. B. ANDERSON and T. H. BYRNES, Am. J. Ophth. **22**:1383 (Dec.) 1939.

A 12 year old Negro complained of a slowly growing tumor on his left eye, present for one year. At the time of examination it was interfering with closure of the lid. Examination revealed an irregularly lobulated, pinkish red growth protruding from beneath the lower lid, near the external canthus. It was pedunculated and was attached in the fornix by a broad base. It resembled the fungoid granulation seen following curettement of a chalazion. It was removed and sent to the laboratory, where a diagnosis of conjunctival rhinosporidiosis was made.

W. S. REESE. [ARCH. OPHTH.]

RHINOSPORIDIOSIS. E. W. GRIFFEY, Am. J. Ophth. **22**:1389 (Dec.) 1939.

Griffey reports the case of a 10 year old white boy with a small strawberry-colored mass on his right caruncle. The boy lived on a farm and helped to care for horses and cows. The mass was solid, nodular and encapsulated and was attached to the upper edge of the caruncle by a thin stalk. It was 12 by 10 by 16 mm., and it prevented the lids from closing. It was excised and sent to the Army Medical Museum, where a diagnosis of rhinosporidiosis of the scleral conjunctiva was made.

W. S. REESE. [ARCH. OPHTH.]

THE RESPONSIBILITY OF THE PEDIATRICIAN IN REGARD TO CHILDREN'S EYES. BRITTAIN FORD PAYNE, New York State J. Med. **40**:1591 (Nov. 1) 1940.

Pediatricians should be able to recognize obvious ocular difficulties, such as defective vision, external diseases and strabismus. They should understand the importance of lighting and posture in reducing eyestrain. Moreover, they should know something about diagnosing reading problems and about the benefits of sight conservation classes. Payne urges that more careful ocular examinations be made.

AIKMAN, Rochester, N. Y.

DISTRIBUTION OF SULFANILAMIDE IN THE OCULAR FLUIDS AND TISSUES AFTER LOCAL APPLICATION. S. Y. P'AN, Proc. Soc. Exper. Biol. & Med. **46**:31 (Jan.) 1941.

In this study 100 mg. of powdered sulfanilamide was inserted into one conjunctival sac of each of 17 albino rabbits. After one hour the concentration of this drug was determined in the conjunctiva, cornea, sclera, lens, vitreous humor and chorioretinal layers in both eyes. Practically no sulfanilamide was found in the untreated eyes or in the blood stream, whereas in the treated eyes these concentrations were present (expressed in milligrams per hundred grams): cornea, 185.4 ± 13.2; conjunctiva, 89.8 ± 14.0; aqueous humor, 54.8 ± 5.3; sclera, 23.3 ± 4.6; chorioretinal tissue, 12.3 ± 1.2; lens, 8.7 ± 1.8, and vitreous humor, 1.1 ± 0.2. Except in the vitreous humor, lens and chorioretinal tissues the concentrations attained in the eye tissues were greater than those obtained by the oral administration of the drug. This method of application has been used with some success in the treatment of trachoma and gonorrhea.

HANSEN, Minneapolis.

ORAL TREATMENT OF TRACHOMA WITH SULFANILAMIDE. F. JASSERON and G. MORARD, Presse méd. **48**:234, 1940.

Jasseron and Morard call attention to the oral treatment of trachoma with sulfanilamide and point out that in their experience this substance gave the best results in the chemotherapeutic treatment of trachoma. The authors treated nearly 200 patients. Subjective symptoms, such as pain, photophobia and lacrimation, disappeared in forty-eight hours; pannus and infiltration of the cornea were reported in eight days; corneal ulcers acquired epithelium in thirty-six hours; cicatrization was accelerated, and clinical recovery took place in three weeks in 75 per cent of the cases. Secondary infections with Week's bacillus, diplobacilli of Morax, pneumococci and gonococci were sterilized in four days. The authors recommend for adults 20 Gm. in thirteen days, for children aged from 8 to 12 years 12 Gm. in twelve days, and for children aged from 4 to 8 years 7 Gm. in twelve days, in decreasing doses. Limited local treatment is advised.

J. A. M. A.

CLINICAL AND ANATOMIC RESEARCH ON A HITHERTO UNKNOWN DOMINANTLY INHERITED DYSTROPHY OF THE CORNEAL EPITHELIUM. A. MEESMANN and F. WILKE, Klin. Monatsbl. f. Augenh. **103**:361 (Oct.-Nov.) 1939.

The authors render a detailed report on dystrophy of the corneal epithelium in three families, the genealogic trees of two of which are given. The divers manifestations in several generations of these families are described in detail and are well illustrated by seventeen pictures, some of them colored, showing the appearance with the slit lamp and with the microscope.

This type of dystrophy of the corneal epithelium, hitherto unknown, is well defined. Its differentiation from the three accepted types and from several special types of hereditary dystrophy of the cornea is discussed. Some of the essential features are dotted and vesicular opacities in the corneal epithelium, observed with the slit lamp, with slight roughness of the corneal surface and pain recurring in attacks. The disease begins in early childhood and progresses at intervals up to advanced age. The visual disturbances are moderate, hardly ever leading to invalidism. The authors report that the deeper strata of the cornea were involved in only 3 patients, who presented linear, curved or striated opacities in or about Bowman's membrane. The corneal nerves were not disturbed. Simple dominant heredity was evident in 34 persons of the two genealogic trees. Histologic examination showed epithelial dystrophy, with its typical epithelial changes, and glycogen stored in the cells. Some of the patients had secondary corneal opacities, caused by eczema; they presented unusually early yellowish discoloration of the scars, described previously in another connection. Hyaline globules were found

in the corneal propria only in some instances; differential staining proved them to be related to elaidin. The epithelial dystrophy was especially well developed beneath the yellowish scars. K. L. STOLL. [ARCH. OPHTH.]

DISK-SHAPED DEPOSIT OF CRYSTALS IN THE CENTER OF THE CORNEA, A HEREDITARY DISEASE: REPORT OF CASES. W. F. SCHNYDER, Klin. Monatsbl. f. Augenh. **103**:494 (Oct.-Nov.) 1939.

The author describes 4 cases of disk-shaped deposits of crystals in the center of the cornea and renders an anamnestic account of 2 other members of the same family, similarly afflicted. The deposits began in early childhood, increased but slightly during life and never caused any inflammatory or other irritations. The deposits were located in the outer parenchyma, directly beneath Bowman's membrane. In every case a white "limbus belt" (type I of Vogt) was noted at the nasal and temporal limbus, within the area of the palpebral fissure. The disease, first described in 1927, represents a hitherto unknown type of corneal degeneration which is inherited dominantly. K. L. STOLL. [ARCH. OPHTH.]

PRIMARY GLIOMA OF THE OPTIC NERVE: REPORT OF A CASE. F. WAGNER, Klin. Monatsbl. f. Augenh. **103**:606 (Dec.) 1939.

A girl aged 5 years showed exophthalmos of the left eye for two and one-half years prior to consultation. A tumorous prominence was noted in the nasal portion of the retina, and closely adjoining it were a number of small choroidal foci and a large one, as well as some preretinal hemorrhages. The roentgenogram revealed widening of the optic canal; the sella appeared normal. Neurologic examination and an encephalogram showed no signs of intracranial involvement by the tumor. The child died from diphtheria twelve days after admission to the hospital.

Histologic examination of the left eye, with the tumor, the optic nerve and the chiasm, is recorded in detail. The tumor was a typical primary glioma of the optic nerve. The identity of glioma and myxoma, myxosarcoma and fibrosarcoma is discussed. The terms gliomatosis and fibrogliomatosis of the optic nerve are considered incorrect by the author. K. L. STOLL. [ARCH. OPHTH.]

THE INFLUENCE OF VITAMIN A DEFICIENCY ON THE DEVELOPMENT OF RECURRING SEASONAL ALLERGIC KERATOCONJUNCTIVITIS (SCROFULOUS?). J. FRONIMOPOULOS, Klin. Monatsbl. f. Augenh. **104**:1 (Jan.) 1940.

The author presents the result of his detailed clinical research with vitamin A in various forms, including synthetic preparations. A number of tables are added. He found relative A hypovitaminosis coupled with undernourishment in the majority of 41 patients. The presence of the hypovitaminosis was established by measuring the vitamin A content in the blood serum and by determining the dark adaptation. Keratinized epithelial cells, observed by Sweet and K'ang, could not be detected in the smears taken from the bulbar conjunctiva for determination of the hypovitaminosis. The vitamin A content in the blood frequently rose, even without administration of the vitamin, as soon as the ocular inflammation had subsided, but it never reached the physiologic standard. Recurrences were often observed in these patients, whereas they did not take place in patients with allergic (scrofulous) keratoconjunctivitis in whom the serum content was normal after administration of vitamin A. This disease may develop in a few persons with tuberculous allergy in the absence of A hypovitaminosis. A physiologic content of vitamin A in the blood and improvement of the dark adaptation were observed after daily injections of 12,000 to 48,000 international units of vitamin A for several days. Ocular inflammation disappeared simultaneously in most patients. There were some recurrences notwithstanding this therapy. Allergic (scrofulous) keratoconjunctivitis was far more frequent directly after the first World War, as

a result of improper nutrition, than in recent years. Because of vitamin A deficiency the epithelial cells of the conjunctiva and the cornea lose their physiologic function and defensive property. K. L. STOLL. [ARCH. OPHTH.]

Skin Diseases; Allergy

ALLERGIC ECZEMA OF INFANCY AND CHILDHOOD: APPLICATION OF SKIN TESTING. HYMAN MILLER, GEORGE PINESS and WILLARD F. SMALL, California & West. Med. **54**:267 (May) 1941.

The technic of cutaneous tests is discussed and the need for complete investigation emphasized. In the cleaning of testing materials the ordinary boiling or sterilization is ineffective in destroying the proteins, so that false positive reactions may be observed unless glassware is cleaned with acid cleaning solution and the needles and other metal parts with strong alkali so as actually to destroy the contaminating protein. In certain cases, all the cutaneous reactions may be negative; consistently negative reactions were observed in 5 per cent of 138 cases of allergic eczema. Owing to contamination of the test sites or to urticaria factitia, all the reactions may be positive. There may be negative reactions to proteins which are known to cause clinical symptoms, while certain positive reactions may be of no clinical significance.

Of 60 cases of allergic eczema in which one could be certain of the causation, in 40 per cent the eruptions were caused by foods alone, in 20 per cent by pollens alone and in 11 per cent by epidermal allergens. In the other 29 per cent there was a combination of allergens. DAVIS, San Francisco.

THE HISTAMINE THERAPY OF ALLERGIC DISEASES: I. ASTHMA AND VASOMOTOR RHINITIS. LAURENCE FARMER, J. Lab. & Clin. Med. **26**:802 (Feb.) 1941.

The author reports 23 cases of either asthma or rhinitis or both which have been treated with solution of histamine phosphate subcutaneously. His results have been very encouraging, and he feels that further study is warranted. He believes that some of the failures of histamine therapy have been due to too large doses of the drug. GARD, Galveston, Texas.

SKIN MANIFESTATIONS DUE TO SULFANILAMIDE AND ITS DERIVATIVES. ARTHUR M. GREENWOOD, New England J. Med. **224**:237 (Feb. 6) 1941.

The first manifestations of the toxic type of eruption are shown by a faint, finely papular rash on the arms—perhaps accompanied by mild itching and fever. If administration of the drug is continued, the rash spreads and becomes maculopapular, scarlatiniform or morbilliform.

The purely allergic effect is shown early in the course of administration of sulfanilamide by intense itching, sneezing, lacrimation and dyspnea, with edema of the lips, eyelids and face. The eruption may be urticarial, hemorrhagic or bullous. Patch and scratch tests with the drug may give positive results.

The allergotoxic effect, that of gradual sensitization, ordinarily appears later in the course of therapy—from the seventh to the fourteenth day of average dosage of sulfanilamide. The eruption is generally maculopapular and is accompanied with pruritus and urticarial lesions, with fever and, in some cases, with leukocytosis. Resumption of sulfanilamide treatment after cessation and the disappearance of the rash is quite certain to bring on a recurrence of the reaction.

All reports and observations show the multiform character of sulfanilamide rashes. The eruption is likely to occur in from 2 to 6 per cent of the cases in which average dosage is used and in about 30 per cent of the cases in which intensive treatment is given. It has been shown that sulfanilamide in certain con-

centration and in certain persons is a photosensitizing agent and that in such patients the rash is confined to exposed surfaces, or is more intense over such areas.

In the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) apparently a somewhat higher incidence of cutaneous reactions is to be expected. Haviland and Long report an incidence of eruption of 12.8 per cent and state that the rashes fall in three groups—maculopapular, urticarial and those like erythema nodosum. This last group has not been reported in connection with sulfanilamide or sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) medication.

GENGENBACH, Denver.

PINK DISEASE: A CONSIDERATION OF THREE ETIOLOGICAL POSSIBILITIES. F. W. CLEMENTS, M. J. Australia **2**:430 (Nov. 2) 1940.

Clements points out that during the last few years three widely different possible causes have been advanced for pink disease: (1) spores of a cereal smut; (2) vitamin B_1 deficiency; (3) a neurotropic virus. Although smut-infected cereals may act as the etiologic factor of acrodynia in Jugoslavia (Mayerhofer and associates), there is no evidence to suggest that this agent plays any part in the causation of the disease in Australia. The fact that infants who contract pink disease are often well nourished and have developed normally up to the time of the onset of the illness and the fact that infants known to be suffering from vitamin B_1 deficiency do not have pink disease would seem to exclude vitamin B_1 deficiency as the cause of the disease. The anorexia of pink disease actually leads to the depletion of the body's reserve of vitamin B_1. In these circumstances pyruvic acid and similar substances tend to accumulate in the cells of the body, further interfering with metabolism. Administration of vitamin B_1, especially by injections, brings about removal of these toxic substances and hence relieves the symptoms and signs not due to the primary disease per se. There is little evidence to support the neurotropic virus theory except that the disease is apparently mildly contagious and occurs in definite epidemics.

GONCE, Madison, Wis.

PINK DISEASE TREATED BY INTRAMUSCULAR VITAMIN B_1: A REPORT OF EIGHT CASES. JOHN DUNCAN HAY, Practitioner **146**:264 (April) 1941.

A study of this series suggests that in some cases pink disease may respond to intramuscular vitamin B_1 therapy, but that such a result must not be expected in all. Such a finding can be satisfactorily explained only by a knowledge of the cause of the condition, which is not at present available. On the vitamin deficiency theory, it may be suggested that in cases in which there is no response to treatment enough vitamin has not been given; or, alternately, that changes have taken place in the tissues which are, at any rate temporarily, irreversible, or, finally, that secondary infection, such as Vincent's infection of the mouth, is interfering with the action of the vitamin. On the infective theory, the successes of vitamin therapy may be attributed to its ability to raise the resistance of the body to the infection, especially in the cardiovascular and nervous systems; and the failures, to the presence of an infection too severe to be dislodged by an increase in bodily resistance alone.

Whatever may be the true explanation of the part vitamin B_1 plays in this interesting disease, it would seem wise to continue to administer it intramuscularly in the hope of relieving some patients and in others preventing the disease from becoming severe. It would also seem advisable to give the other fractions of vitamin B. By this treatment one not only would be adopting the only method which at present appears able in some instances to cause marked improvement but would, in addition, be providing further material on which to base a more accurate knowledge of the role of vitamin B deficiency in the causation of the disease.

AUTHOR'S SUMMARY.

HERPES ZOSTER ACCOMPANYING MENINGITIS IN INFANCY. ISTVÁN BRÜNDLMEIER, Orvosi hetil. **84**:259 (May 18) 1940.

A 9 month old infant with the symptoms of meningitis was observed. The infant also had bilateral otitis media and on the left side a patch of herpes zoster a handbreadth wide, stretching forward on the trunk from the spine. The cerebrospinal fluid was water clear, but the Pandy reaction was positive and there were 200 lymphocytes per cubic millimeter. The occurrence of herpes zoster with meningitis is not very rare, but it has not yet been observed in infancy. The infant recovered completely in two weeks.

GÖTTCHE, Budapest, Hungary.

ADIPONECROSIS AND COLD. H. HAXTHAUSEN, Nord. med. **27**:1174, 1940.

According to H. Haxthausen, severe cold can cause a peculiar indurated infiltration of the subcutaneous fatty tissue of the face (cheeks and chin), especially in small children. Histologically there is necrosis of the fatty tissue accompanied by inflammatory reaction, with lymphocytes in the supporting tissue of the fatty layer and a few lipoblasts—the latter being evidence of the regeneration process. The condition develops within a few days of severe exposure. Although the symptoms differ from those of frostbite and chilblains, the latter may both occur in addition to the necrosis. Clinically, as well as histologically, the picture resembles that of so-called adiponecrosis neonatorum, which may be brought about by mechanical trauma at birth. In either case the necrosis of the fatty tissue is seen in very early life; in later years the tissues seem to be able to withstand cold and trauma better. The prognosis is favorable. In cases reported by the author there was spontaneous remission within a few weeks.

ABT, Chicago.

Surgery and Orthopedics

FAMILIAL PES CAVUS AND ABSENT TENDON-JERKS: ITS RELATIONSHIP WITH FRIEDREICH'S DISEASE AND PERONEAL MUSCULAR ATROPHY. JOHN P. SPILLANE, Brain **63**:275, 1941.

Spillane made a study of a family group in which 21 members presented signs of degeneration of the spinal cord. Of these, 16 had the syndrome of Roussy and Lévy, consisting of bilateral pes cavus, absence of tendon jerks and difficulty in walking. Four of the 16 patients showed as well an explosive type of dysarthria. The abnormality usually becomes evident in infancy, with delay in learning to walk, clumsiness and frequent falls. The foot deformity develops early during childhood. Running and jumping become impossible. In most of the 16 cases described, slight clumsiness of the hands and atrophy of the thenar and hypothenar eminences were observed. The condition usually progresses slowly during adult life, and a slight amount of functional adaptation may occur.

Three of the 21 patients presented a typical picture of Charcot-Marie-Tooth muscular atrophy. Another, with a fairly typical example of Friedreich's disease, showed marked kyphoscoliosis, bilateral pes cavus, absence of knee and ankle jerks and extensor plantar reflexes.

Thus, in one family group there occurred cases of the syndrome of Roussy and Lévy, of Friedreich's disease and of the Charcot-Marie-Tooth type of muscular atrophy. In the absence of pathologic evidence, Spillane concludes that the syndrome of Roussy and Lévy represents a subgroup of the heredofamilial degenerations of the spinal cord and cerebellum of which Friedreich's disease and the Charcot-Marie-Tooth muscular atrophy are fully developed forms.

MASLAND, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

THE ROLE OF VITAMIN C IN WOUND HEALING. ALAN H. HUNT, Brit. J. Surg. **28**:436 (Jan.) 1941.

The author reviews the place collagen holds in the histology of wound healing and then discusses the references in the literature to the function of vitamin C in the formation of collagen.

An investigation was carried out on guinea pigs which had received a diet deficient in vitamin C. Wounds on these pigs healed more slowly than did wounds on the controls.

The second part of the investigation was a review of the cases of 28 surgically treated patients who had died of some gastrointestinal condition and might be expected to have some vitamin C deficiency. In 8 the surgical wounds showed a deficiency in the formation of collagen resembling that in the subscurvy guinea pigs.

The author recommends 1 Gm. of ascorbic acid a day for 3 days in vitamin C–deficient patients and 100 mg. a day to maintain saturation of the vitamin. Its use is urged before and after operation, especially (1) when clean and quick healing of a wound is particularly desirable, (2) when a major abdominal operation is performed, (3) when a hollow viscus has been opened, (4) when postoperative complications are anticipated, (5) when there is evidence of a nutritional deficiency or (6) when there is serious injury.

KEITH, Toronto.

Miscellaneous

THE WET NURSE IN FRANCE IN THE EIGHTEENTH CENTURY. T. G. H. DRAKE, Bull. Hist. Med. **8**:934 (July) 1940.

The percentage of infants nursed by wetnurses in the eighteenth century was enormous. According to one of the sources—"Details of some Establishments of the City of Paris . . ." by Lenoir (1780)—at the most one thirtieth were nursed at the mother's breast. By means of many beautiful illustrations and reproductions of documents one learns about the recruiting of wetnurses by special agents, the *meneurs* and *meneuses*. Often the former carried on this work only as a sideline. In order to regulate the traffic in wetnurses and to safeguard the nurses as well as the employers, *meneurs* had to be certified, and they were required by law to register and lodge the prospective nurses at one of the official bureaus. Many laws were enacted to curb the numerous abuses. For example, a nurse was allowed to take only one infant; separate beds were required for the nurslings in order to avoid accidental suffocation; provision had to be made for the care of the infants on their trips; nurses were required to obtain certificates for the infants for the purpose of supervision by the parish priests.

In contrast to the haphazard selection and the poor pay of wetnurses for ordinary citizens, we find that extreme care was used in the selection for the nobility and particularly for the royal family. The author presents documentary evidence as to high positions such wetnurses reached when the royal children thrived on their milk.

ROSENTHAL, St. Paul.

A QUASI-AUTOBIOGRAPHICAL CASE HISTORY OF AN ANCIENT GREEK CHILD. BRUNO MEINECKE, Bull. Hist. Med. **8**:1022 (July) 1940.

Meinecke presents an analysis of a Greek sepulchral inscription found at Smyrna, apparently dating from the third or second century B.C. The child, which had lived only 4 years, 5 months and 20 days, had suffered first from an ailment about the testicles, of which the father cured him, and later from a suppurative disease of the foot, which was cured surgically by friends of the father. He finally succumbed to an intestinal ailment accompanied by distention and general wasting. The author believes that the father, Anthimus, must have been a physician, because of the many technical terms in the text, the fact that he treated the child himself—at least during the first ailment—and the fact that it

was he who bathed the baby post partum. It is not unlikely that he even delivered the baby himself.

As to the three ailments, the author comes to the conclusion that all were manifestations of tuberculosis. The testicular infection apparently showed a spontaneous remission, while the tuberculosis of the metatarsal bones showed improvement or healed after surgical removal of the diseased portions.

The complete Greek text of 27 dactylic hexameters, together with a translation, is included in the article. ROSENTHAL, St. Paul.

THE RELATION OF FETAL ACTIVITY TO THE ACTIVITY OF THE MOTHER. GERTRUDE RAFFEL SCHMEIDLER, Child Development **12**:63 (March) 1941.

From approximately five and one-half to seven and one-quarter months of pregnancy, the author recorded the location, intensity and number of fetal movements occurring during one hour. There were forty-two such experimental hours, thirty-three of which followed normal waking activity and nine of which followed a night's sleep.

The number of fetal movements per hour increased during pregnancy. The average number of movements at the end of the sixth month was 77.3; at the beginning of the eighth month it had risen to 242.

There was an inverse relation between the degree of maternal activity preceding the session and the number of fetal movements during the session. Following maternal activity, the number of fetal movements was smallest during the first five minutes; it then gradually increased until after about thirty minutes there were approximately as many movements as there were after sleep. Even one-half hour of activity on the part of the subject was sufficient to produce this effect.

AUTHOR'S SUMMARY.

NICOTINE POISONING IN A CHILD. RICHARD W. CRAGG and ARNOLD E. OSTENBERG, J. A. M. A. **115**:600 (Aug. 24) 1940.

A 4½ year old boy suddenly became ill with nausea, vomiting and lassitude. The following day, after drinking some fluids, he had a convulsion and died about one-half hour after taking the fluids.

Postmortem evidence and a retracing of the history incriminated some snuff that he had eaten. There were inflammatory changes in the lining of the stomach and an incidental polyp in the colon. HEERSMA, Kalamazoo, Mich.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, Nov. 18, 1941

JAMES H. WALLACE, M.D., *President, in the Chair*

Panel Discussion of Serum Treatment of Poliomyelitis

DR. CLIFFORD G. GRULEE, *Chairman*

Effectiveness of Serum Therapy for Poliomyelitis from the Laboratory Standpoint. DR. H. J. SHAUGHNESSY, Chief, Division of Laboratories, Department of Public Health, State of Illinois (by invitation).

Experiments conducted about eleven years ago on serum therapy for poliomyelitis gave completely negative results. In those days very small amounts of serum of low potency were injected intraspinally. It was realized that larger doses of serum were required, with a less drastic route of administration. Further experiments were planned but were not carried out because of lack of animal material (monkeys). It was realized, however, that the virus was extremely potent, causing more than 90 per cent fatalities in monkeys, and that the portal of entry, the potency of the serum and the amount to be given were of utmost importance. These factors have not always been taken into account in assaying the value of serum therapy.

If the value of any antiserum rested on laboratory evidence, it is probable that neither diphtheria antitoxin nor pneumonia serum would be used by clinicians today. The demonstration of their value has been made by clinicians and not by bacteriologists. The disease against which the value of antiserum has been demonstrated in the laboratory, tetanus, is one of the few diseases for which clinicians hesitate to use serum, feeling it to be of little value. While there is little true evidence from laboratory study of the therapeutic effect of poliomyelitis convalescent serum in animals, this cannot be accepted as meaning that it is of no value. The rhesus monkey is not well adapted to this type of investigation; the factor of time, the route of inoculation and the strain of the virus must be taken into consideration. Negative evidence cannot be accepted.

Much work has been carried out on the protective value of convalescent serum. It has been shown that pneumonia convalescent serum injected intravenously protected the monkey against subsequent intravenous inoculation of virus, and that the presence of serum antibodies in the circulation acted as a barrier to further dissemination of the virus. Similar semitherapeutic effects have been obtained in experiments with the virus of poliomyelitis. There has been a feeling, however, that serum therapy for virus diseases is not of value. This is based on the fact that viruses are intercellular parasites; they remain within cells and produce their principal damage in cells. It is known also that once the virus has invaded cells it cannot be neutralized by serum unless the cells are dead. There is no reason, however, why serum cannot prevent the intracellular spread of the virus by building a moat around each cell. The method of prevention of spread from cell to cell is recognized for bacterial diseases and those in which toxin is liberated. If it is effective for those diseases, why not for virus diseases? There is evidence that serum treatment of influenza in mice had prevented further damage to cells. With regard to equine encephalomyelitis, for which the production of potent antiserums is relatively easy, it has been shown that administration of serum at the first sign of the disease protects animals against further invasion of virus in practically 100 per cent of cases; even after the onset of paralysis, it was possible to save many of the animals. Further, after recovery the animals had acquired active immunity.

To summarize: The evidence for the value of serum treatment of most bacterial diseases has come from clinical investigation rather than from laboratory tests; the evidence of the value of convalescent serum in the treatment of poliomyelitis will probably come from clinical investigation. Most laboratory tests for use with bacterial diseases are considered satisfactory when it has been proved that the serum is of protective value against the etiologic agent; this evidence should be accepted for convalescent serum. The available evidence from experiments with other virus infections indicates that there is no theoretic reason why serum treatment of early poliomyelitis should not be successful, if the factors of potency of serum, route of infection, and dosage are kept thoroughly in mind.

Theoretic and Practical Considerations Concerning Treatment of Poliomyelitis. Dr. J. A. Toomey, Division of Contagious Diseases, City Hospital, Cleveland (by invitation).

In treating poliomyelitis, one has to consider the disease in three stages: (1) the symptoms, (2) the disease itself and (3) convalescence. During the early stage and before the onset of paralysis, approximately 30 to 50 cc. of poliomyelitis antiserum may be used intramuscularly and the gastrointestinal tract evacuated. There is some question whether this specific therapy is of value. The treatment in the paralytic stage depends on the muscles involved, whether they are muscles of the body or muscles supplied by the cranial nerves. If there are paralyses of the body, evacuation of the gastrointestinal tract should be done at once by the use of salts internally and enemas three or four times a day. If the bladder is paralyzed, it should be washed out. Convalescent serum has been used (50 to 100 cc. intravenously), but its efficacy is debatable. For more than twenty years we have treated our patients early, giving active and passive motion to the paralyzed muscles, according to the recommendation of Feiss more than twenty-five years ago. Sister Kenny has advocated early treatment. The other method of treatment is the orthopedic method of putting the patient at complete rest. Other conditions are treated symptomatically.

If the intercostal muscles and diaphragm are paralyzed, respirators are needed. The treatment during convalescence depends on whether one believes in treating the patient early or feels that it is better to leave him alone. We favor early treatment on the theory that the most important thing is to keep the muscles in good condition. We do not think it advisable to inject either hypertonic or hypotonic solutions or large amounts of fluid—even specific fluids—intravenously. After the quarantine period is over, the orthopedic surgeon ordinarily takes charge of the case. It is wise to have him see the patient as soon as the diagnosis is made.

Patients with bulbar poliomyelitis have to be treated carefully. The head of the bed should be lowered and the foot raised; mucus should be aspirated from the throat regularly; about 500 to 800 cc. of fluid should be given subcutaneously for the first few days and nothing given by mouth; enemas should be administered frequently and dextrose solution given by vein; convalescent serum may be employed if one wishes to use it.

Clinical Evaluations of the Effectiveness of Human Convalescent Serum in Poliomyelitis. Dr. Archibald L. Hoyne, Medical Superintendent, Municipal Contagious Disease Hospital.

During the past twenty-five years at Cook County Hospital, and for part of that time at Municipal Contagious Disease Hospital, at least four different serums have been used in the treatment of poliomyelitis, and the results were all similar. The conclusions reached were based entirely on observations, and observations, regardless of scientific reasoning, are sometimes very good. Animal serum was used as far back as 1917; convalescent or normal serum has been used for only about ten years in these hospitals.

Those who advocate the use of poliomyelitis convalescent serum stress early treatment as essential for success and administration of serum before the development of paralysis. Large quantities of serum are sometimes advised for the

purpose of overcoming toxemia; an abrupt decline in fever following administration of serum is considered evidence that the serum has accomplished its purpose.

It is claimed that if serum is given during the so-called preparalytic stage, paralysis will be prevented; that if it is given during the acute stage, even though some paralysis is already present, further extension will not occur; that serum treatment for patients who have paralysis results in more rapid convalescence with less paralysis than is experienced by those who do not have serum. It has been inferred that extensive use of convalescent serum can be a factor in lowering the death rate.

During the recent outbreak of poliomyelitis in Chicago, the health department records showed 157 cases and only 6 deaths, a fatality rate of approximately 3.8 per cent. This applies only to cases in the city. At Municipal Contagious Disease Hospital 87 patients were treated, with 4 deaths, or a case fatality of 4.6 per cent. At the contagious disease department of Cook County Hospital, 69 patients were admitted, many from rural or suburban districts. There were 4 deaths in this group, a fatality rate of 5+ per cent. About 30 per cent of the patients at the Municipal Contagious Disease Hospital received serum; about 50 per cent of those at the County Hospital received serum.

It is interesting to note that of the patients who did not have paralysis at the time of admission to either institution and who were not given serum, none had paralysis later, whereas paralysis developed in several who did receive serum. On numerous occasions in the past it has been thought that one serum or another was beneficial; improvement was commonly noted, but not always. However, favorable conclusions in respect to any form of serum therapy are likely to be deceptive. Patients not treated with serum show equally good results.

It has been concluded, therefore, that serum therapy does not reduce the death rate, that it does not prevent the development of paralysis, that it does not check the spread of paralysis when present and that it does not lessen the amount of residual paralysis.

Clinical and Experimental Observations on the Use of Human Convalescent Poliomyelitis Serum. DR. S. O. LEVINSON, Director, Samuel Deutsch Convalescent Serum Center (by invitation).

Much of the confusion in the controversy on poliomyelitis has been occasioned by groundless statements and questionable theories. The so-called control studies of the past have formed the bulwark of arguments against the use of convalescent serum. That published by Park in 1932, based on the outbreak of poliomyelitis in the city of New York in 1931, has been most frequently cited. From personal observation of serum therapy conducted during that period, the following comments were made: (1) The treatment dose was around 60 cc., a second dose of 20 or 40 cc. occasionally being given on the following day; (2) serum was administered to the sickest patients.

The report of the special committee from the Academy of Medicine stated that "the untreated group was indeed a much milder group than the treated group." In Park's report there was an analysis of the outcome based on the severity of illness as estimated by the physician. The patients with mild poliomyelitis had a 5 per cent incidence of paralysis involving several to many muscles. The fairly ill group had a 14 per cent incidence of such paralysis; the very ill group, a 55 per cent incidence. The mortality rates were 2 per cent for the patients with mild poliomyelitis, 2.25 per cent for the fairly ill group and 27 per cent for the very ill patients. Of 4 patients recorded as dangerously ill by the physicians, 3 died. It is obvious from the foregoing observations that if the untreated group had the disease in a much milder form than did the treated group, the study could not be called a control study, and if serum were of no value the treated group should have had much poorer end results. Actually, this was not the case. Further, there was question as to the accuracy of recording cases, due to inadequate examinations and improper classifications, which make the result of this study highly dubious. The Committee of the Academy of Medicine concluded that "the results of this study are inconclusive."

The effect of the report was an almost universal discarding of a measure which had been thought valuable. In the intervening years no good control study has been performed. Practically all subsequent reports show the same fallacy of inadequate therapy, showing an incidence of paralysis of 20 to 30 per cent, with administration of small doses of serum. The report of Dr. Hoyne presented tonight, however, is an exception. His results are remarkable from the viewpoint that none of the untreated patients in the preparalytic stage had any paralysis later. It is possible, of course, that in a larger series the final incidence of paralysis would be comparable to that noted in other studies.

For the past ten years every acutely sick patient in the preparalytic stage of poliomyelitis who has come to attention in various hospitals throughout the city has been treated. The diagnosis of preparalytic poliomyelitis was not made without careful physical and neuromuscular examination, supplemented by spinal puncture yielding fluid showing characteristic changes. Furthermore, for the last four years in most instances spinal fluid and/or blood was inoculated into guinea pigs or mice to rule out lymphocytic choriomeningitis. Treatment consisted of intravenous administration of 100 to 300 cc. of human convalescent poliomyelitis serum, repeated every twenty-four hours in the average case and every twelve hours in cases of fulminating poliomyelitis until signs of acute illness had subsided.

The total of preparalytic patients thus treated numbers 298. Of these, 63 per cent recovered with no evidence of paralysis; 25 per cent had transient weakness which disappeared during the three week isolation period; 9 per cent had mild paralysis, not incapacitating, which usually cleared up within three to six months; 2.3 per cent had moderate or severe paralysis, and 1 per cent died. It would not be correct to compare this with reports showing an incidence of paralysis of 20 to 30 per cent, but it is felt that this low incidence of significant paralysis in this series of 298 patients speaks for itself. No attempt has been made to evaluate the results of therapy in paralytic patients. However, a 32 per cent mortality in 140 acute patients with bulbar or bulbospinal poliomyelitis is significantly lower than former experience with this type.

The following considerations are important:

1. Cells already invaded by virus probably cannot be affected by serum.

2. Nerve cells may be invaded by virus, but death of the cells may be delayed so that objective evidence of cell involvement is postponed.

3. Human convalescent serum is of low potency.

It is obvious that the most beneficial effects may be expected if serum is given early in large amounts by the intravenous route; the injections must be repeated, because there is variability in degree of infection and severely ill patients may require very large amounts. Paralysis may appear even after treatment has started, owing to death of nerve cells already invaded at the time of institution of serum therapy. If it occurs, it is seen within twenty-four hours after serum therapy has been started. There is good evidence that serum will neutralize virus in transit or at dead cells. Recent work pointing to lymphatic dissemination of virus, possibly from the intestinal tract, would help explain the efficacy of serum.

The controversy should not be closed without further study and evidence. An open mind must be maintained until the issue is scientifically settled. Further laboratory work, based on the natural seat of infection and natural routes of dissemination of virus, must be prosecuted. True control alternate case studies by impartial and unprejudiced observers, giving due recognition to proper dosage, must be carried on. This is too important a subject and the illness is of too grave a nature to discard a therapy without just grounds.

DISCUSSION

DR. ARCHIBALD L. HOYNE: What do you mean, Dr. Levinson, by large amounts?

DR. S. O. LEVINSON: I should say between 200 and 1,000 cc. The disease varies in different patients, and the dose cannot be standardized. However, with

the amounts we are using we believe we are getting good results. Further, administration of even large amounts of serum is not extraordinary.

DR. ARCHIBALD L. HOYNE: Do any statistics show that larger doses are more effective?

DR. S. O. LEVINSON: That question is difficult to answer, because the patients whose condition is more critical get the larger doses of serum.

DR. CLIFFORD G. GRULEE: Is there any evidence that virus will be neutralized in transit and in dead cells?

DR. S. O. LEVINSON: I believe there is satisfactory laboratory evidence for this statement.

DR. ARCHIBALD L. HOYNE: Dr. Brodie attempted to show that in the monkey the virus combined with nerve tissue in five minutes. If that were so, there would be a slim chance of treating patients effectively.

DR. S. O. LEVINSON: The virus is not introduced directly and immediately into the central nervous system in the human infection as it is in the experimental disease in monkeys.

DR. ARCHIBALD L. HOYNE: How does one know a monkey has the disease?

DR. S. O. LEVINSON: The monkey has the specific virus in the central nervous system, paralysis develops and the histologic picture is characteristic of the disease; tests for transmission and serum neutralization are further confirmation.

DR. J. A. TOOMEY: How do you know that the serum did not do harm and give the patients paralysis?

DR. S. O. LEVINSON: We have observed nothing of this kind in an extensive experience with serum therapy.

DR. ARCHIBALD L. HOYNE: Your use of the term "preparalytic" leads to one of our favorite arguments; this term infers that paralysis will occur, but this does not usually happen. How can any one know when a patient is going to have paralysis?

DR. S. O. LEVINSON: I agree with that. I prefer the use of the term "acute poliomyelitis without paralysis." In a large number of cases from many reports, it may well be expected that 20 to 30 per cent of patients will have paralysis if they are not treated. The experience in New York seems to indicate that clinical practice in dealing with the disease can give the clinician judgment as to which patients are more likely to have paralysis.

DR. CLIFFORD G. GRULEE: Were all the cases in your series epidemic cases?

DR. S. O. LEVINSON: Practically all occurred during the summer and fall months, during the time that there was an increased incidence of the disease in the community.

DR. CLIFFORD G. GRULEE: In an epidemic, the ordinary symptoms of poliomyelitis suggest themselves and there is more reason to think one's diagnosis is correct. But in sporadic cases one may observe the same symptoms and yet the condition may not be poliomyelitis.

DR. S. O. LEVINSON: For that reason my associates and I are extremely careful in making the diagnosis. We require a rather characteristic history and symptom complex, with confirmation by lumbar puncture yielding fluid with an increased cell count and a positive reaction for globulin. Since 1937 we have tried to rule out lymphocytic choriomeningitis by inoculating spinal fluid and blood into mice and guinea pigs. I might add that it is rare to find a case of lymphocytic choriomeningitis.

DR. H. J. SHAUGHNESSY: I will bear out Dr. Levinson on that.

DR. J. A. TOOMEY: Any person who makes a diagnosis of lymphocytic choriomeningitis has to prove it. I should like to call attention to a case mentioned by your associate, Dr. Wolf, at a recent meeting, in which a patient treated with large amounts of serum had more and more paralysis.

DR. S. O. LEVINSON: We have never seen anything indicating shock due to action of the serum on the virus, such as is referred to by Dr. Toomey. I want

to make clear that we do not expect to get 100 per cent satisfactory results, and when patients with such fulminating conditions come to us even before paralysis has appeared we may not be able to save them.

DR. J. A. TOOMEY: That has not been my experience. My associates and I have had such reactions. They come on abruptly after the giving of serum.

DR. S. O. LEVINSON: That is strange: Don't these patients with fulminating conditions give a history of illness before paralysis? Although such preceding illness is shorter, we have found that it does occur.

DR. J. A. TOOMEY: But in cases of the nonparalytic type of poliomyelitis fulminating disease does not develop.

DR. S. O. LEVINSON: I agree with you, but in a small percentage of cases the disease does go on to the fulminating type. We feel that the preparalytic stage is shorter in the fulminating type.

DR. J. A. TOOMEY: I think Dr. Levinson has not proved that serum therapy has any efficacy. He reported on 298 cases but had no control series; so one does not know what would have happened if the patients had not been treated.

DR. S. O. LEVINSON: I realize that a study with a control series is the ideal type. Such a study is very difficult to make. It could and should have been performed in New York in 1934 but was not. There have not been sufficiently large epidemics there for us to observe control and treated groups under the ideal conditions Faber has set forth. It is essential that this be done.

DR. J. A. TOOMEY: Then you will admit this is not a life-saving measure?

DR. S. O. LEVINSON: No. I have no way of saying it is or is not a life-saving measure. Scientifically, I should say it is just as life saving as other serum treatment.

DR. J. A. TOOMEY: I question that. The other point I want to make is that a physician is not doing his patient a dis-service when he does not use serum.

DR. S. O. LEVINSON: I think the question of moral or legal responsibility must be considered. If a physician is convinced that serum is of no value he does not have to use it. I should like to compare the use of poliomyelitis serum with the use of antitetanus serum. The circumstances are strikingly similar. Tetanus toxin cannot be neutralized once it has combined with the anterior horn cells. The laboratory evidence is not very convincing. The clinical experience is distinctly controversial. Further, when active symptoms of tetanus develop, much of the toxin has already combined with anterior horn cells. In view of all these conditions, should a physician withhold tetanus antitoxin from a patient with tetanus?

DR. J. A. TOOMEY: I should rather have the patient's wound cleaned out by a surgeon.

DR. S. O. LEVINSON: We are all in agreement that the wound should be properly treated, but I am referring to the treatment of a patient with active tetanus. Would you use antitoxin?

DR. J. A. TOOMEY: Not necessarily; probably, if there might be legal complications.

QUESTIONS FROM AUDIENCE AND ANSWERS

QUESTION 1: I should like to ask Dr. Toomey to describe how he made the diagnosis in his 40 cases of poliomyelitis of nonparalytic type.

DR. J. A. TOOMEY: We have had a number of instances of several cases of poliomyelitis occurring in the same family. The majority of the cases of the nonparalytic type were in this group. During the course of an epidemic, if patients have gastrointestinal upsets, clinical signs of poliomyelitis and an increased cell count (practically always lymphocytes, although we have seen leukocytes), I think it is fair to make a diagnosis of poliomyelitis, especially if there are neurologic signs, such as loss of reflexes.

QUESTION 2: Does Dr. Toomey think the administration of serum by slow continuous drip alters or minimizes its danger?

DR. J. A. TOOMEY: I do not believe it does. I am sure we have killed some patients by giving serum.

QUESTION 3: Will Dr. Toomey tell how much serum he gives intravenously in treating meningitis? Does this amount adversely affect the spinal cord in this disease? What is the physiopathologic nature of this neutralization shock?

DR. J. A. TOOMEY: I really think that not enough attention is paid to paralysis that comes on after injection of serum. My associates and I feel there may be subsequent edema in the cord.

DR. J. A. LEVINSON: With reference to the so-called ill effects from intravenously administered serum, I want to repeat that we have not observed any. Furthermore, we have had occasion in experimental work to introduce large amounts of serum into dogs. We have given up to 300 cc. to a dog weighing 15 Kg. without any ill effects. I believe the adverse effects occur only when serum is improperly prepared.

DR. J. A. TOOMEY: In experiments on dogs hypotonic solutions are injected into animals in shock or with unimpaired mechanism; in poliomyelitis, however, the situation is different, for there is an actual break in the vascular mechanism.

QUESTION 4: Dr. Hoyne, in view of the difference of opinion on the value of convalescent serum, do you advocate stopping its preparation and stopping placing it at the disposal of clinicians by the state?

DR. ARCHIBALD HOYNE: It seems to me it would be very poor policy to have physicians agree that it is of no value and have the state continue to produce it. It would seem that the proper procedure would be to have a commission appointed to reach a decision as to whether or not it is of value. If it is not, its production by the state should be discontinued.

QUESTION 5: Does Dr. Hoyne have any statistics on the number of deaths that occurred at Cook County Hospital or Municipal Contagious Disease Hospital in patients who had or did not have serum?

DR. ARCHIBALD L. HOYNE: It would be unfair to attempt to give an answer to that question and the reply would not mean anything. Practically all the patients who died had had serum, but they did not die because they had serum. It was administered in the forlorn hope that it would do some good.

QUESTION 6: Will Dr. Levinson tell something about the postmortem observations on patients treated with and without serum?

DR. S. O. LEVINSON: In most of the patients the disease was of bulbar type and there was not so much involvement as in the spinal type. So I do not think any conclusions can be drawn on the basis of histologic observations. A number of years ago Harmon attempted to isolate virus from the cords of patients who died of poliomyelitis. All had received large amounts of serum. He was able to isolate the virus from only a single specimen.

QUESTION 7: Dr. Grulee, don't you feel that until almost infallible diagnostic tests or procedures are available, this question will be unanswered? Certainly at the bedside it is impossible to make a diagnosis in many cases in the early stages.

DR. CLIFFORD G. GRULEE: I should have answered that question differently this afternoon. However, in summing up I should like to say that apparently there is no evidence from animal experiments, so far as has been brought out, that there is very much protection against poliomyelitis by the use of serum therapy. I would also say that it has been brought out that there is no proof that serum is beneficial, and that it has been suggested its effects may be quite the opposite of what one expects. There may be some question in the minds of some of us here as to whether we were justified in using serum in some cases of poliomyelitis.

Book Reviews

In Defense of Children. By Bert I. Beverly, M.D. Price, $2. Pp. 233, with 12 illustrations. New York: The John Day Company, 1941.

This robust little book contains eleven chapters dealing with the ordinary problems of the growth and development of ordinary children. Its tendrils reach out into every aspect of the child's life, but the main root is in terms of seeing the problem of maladjustment as the child's vain attempt to fit his strong biologic urges into the cramped forms that society would have them take. If there were only some way of letting the child be what he was intended to be, there would be much less unhappiness.

So chapter 1 bids one see the child as he is, rather than only as adults wish him to be. It's rather a nice sermon on tolerance. Chapter 2 states the corollary that the child is himself a fairly safe guide as to what he needs in food; what he will accomplish by way of growth. Chapter 3 ties these ideas together; and chapter 4 vigorously points to parents the extent to which their lives affect their children. Chapter 5 is excellent on jealousy. Chapter 6 covers once more the weary road as to what is education as opposed to what are the symbols (grades, marks, etc.) of education. Chapter 7 is on discipline; chapter 8 deals with responsibility and chapter 9 with fears. Chapter 10 takes up adolescence. Chapter 11 is a sort of summary.

There are many outstandingly good things about this book. It is clearly written—no one would ever doubt what Dr. Beverly is writing about or what he is saying about it. The style is staccato, and the volume bristles with statements that tend to be epigrammatic. This has tempted the publishers, who have literally plastered the jacket with quoted phrases that are more sparkling than accurate. The world contains many busy parents who need to be laid low by these nicely poisoned darts; but it contains many more who in honest patience have found that life isn't played with the breezy simplicity of Dr. Beverly's rules.

This business of exhorting the citizenry to keep its shirt on is of importance after the psychiatric barrage of alarm and accusation which blazed for a decade. If one *had* to choose, one would agree with the author that adults harm children much more by what they do for them than by what they don't do. The broken dreams of adult years Dr. Beverly would have one sweep into the discard. As a pediatrician he is dead right. But when he writes a book in defense of parents he will find that if the children are not to be driven to reassemble the broken pieces he must find some other agent for that task. For each person life is too precious to be left strewn about the floor. One can't just preach a calm, objective view as to the offspring when the patterns of adult lives cry out for reassemblage.

Rather better than any other book I know, this volume presents the concept of "the load." This is as good a term as any for the notion that behavior is not necessarily specific to its cause. Dr. Beverly over and over stresses that the child with overwhelming problems ("an overwhelming load") will express this fact in conduct that is dictated by his own vulnerability or that of his environment. Thus failure to make a satisfactory adjustment is only an indication that the child is carrying too much of a load. The character of the behavior is not necessarily indicative of the character of the load. Perhaps this will be the real start of thinking in terms of "the hundred results of school pressure" rather than in the present universal but sterile terms of "the hundred causes of stealing." To start the world thinking about the results of tensions rather than about the causes of conduct, this itself would be rich reward for one book.

And there is another excellent job in Dr. Beverly's clever sandwiching of the simple and the devious. One starts unsuspectingly on a case history to find its

solution in a sentence; equally without warning one finds that the next case has a long and complicated set of factors in it. Pediatricians very much need this—it may do something to their present sharp cleavage between those who think all problems of behavior to be very simple and those who would look for erudite psychiatric help for each.

But there are other matters not so easily accepted.

When psychiatrists (and pediatricians) went into this field of the behavior disorders they bravely set out to do away with blame. One does not *blame* persons for having fever—why should one blame them for stealing or wetting the bed? Well and good—if one would only be true to the theory. What is done in Dr. Beverly's book—and in so many others—is that the object of blame has simply been shifted. There seems to be quite as much moralizing in this volume as in the attitudes of a century ago—only now the show of its disappearance is made through criticism of the parents of the patients instead of the patients. This is not a forward step.

Dr. Beverly begins his summary chapter with the statement "Mental health throughout life can be assured to those babies who are normal at birth (and practically all of them are) if parents, physicians, and teachers have a clear conception of growth and development from birth to maturity and follow a few general principles in rearing them." This is a pretty good summary of the spirit of the book. The statement is incorrect—not to speak of the terrific sense of guilt which it inevitably imposes on countless parents. It smacks very much of the slogan ("Insanity is preventable") with which psychiatry has sold so much of its wares. It is the physician's job to help people—not to increase their burdens of unhappiness by telling them what a good job could have been done had they only come earlier or followed his advice. Dr. Beverly writes in a vein of good common sense, and he has a sort of rugged honesty about life that will help a great many persons. But if countless ages of wise men and fools have not yet mapped out the royal road, I doubt that 216 pages of printed rules will do it.

And the reason they will not is one that besets pediatrics (and a good deal of psychiatry) in most that it does today. In large measure patients turn to pediatricians in perplexity as to "values." This is a new field for the physician, and one in which he has had no training. "What do I want for my child" is not too often today in terms of a way of getting him to eat more spinach. Most families know full well that the spinach will be taken care of, if they could only be at peace as to "what it's all about." Dr. Beverly's reply would be that he does not know any more about that than do his patients—and that therefore he didn't put a word about it in his book. Here, for once, the physician must say "I wish I knew; let's find out." That is a difficult role for him, because any show of ignorance ill fits his traditional relationship with his patients. But I guess that one day it will lead to mental health and that it will do so more surely and more quickly than will "the following of a few general principles."

Books that excite sharp criticism are either pretty bad or pretty good. This volume decidedly belongs in the latter class. It is full of sound advice—written for the parent or physician with that simplicity with which truth always clothes itself. Besides, it's good reading.

Treatment of Infantile Paralysis in the Acute Stage. By Elizabeth Kenny. Price, $3.50. Pp. 285, with 63 illustrations. Minneapolis: Bruce Publishing Company, 1941.

This book becomes of considerable interest because of the publicity concerning its author and her work and because of the favorable reports which some medical observers have made on the results of the Kenny treatment for infantile paralysis. The book will not commend itself to critical readers, but in view of the probable value of the treatment itself it must be read with some generosity. The book is poorly planned and badly written and is very difficult to read. A large part of it is given over to contentious and repetitious statements regarding the underlying

theories which the author has developed about infantile paralysis. The pages abound in reiteration of the phrases "indisputable evidence" and "proof" in support of the author's contentions, but most of the evidence offered is merely a repetition of the statements to be proved or quotations from various writers commending the author's work. Her beliefs are that flaccid paralysis does not occur in infantile paralysis but rather that "spasm" exists in the opponent muscle and that the apparent paralysis is due to an "alienation" of the patient's mind, which makes it impossible to contract the one muscle overextended by spasm in the other. A typical passage of the book appears in an explanation of the difference between contraction and spasm. It is stated: "To explain the difference between a contraction and a spasm, I wish to state the term spasm is used when there is a series of contractions felt in the part of incoordinate contraction of the part. These contractions are rapidly repeating (repeated?) and become exaggerated at attempted assistance to bring about a condition of relaxation." The conception of spasm in one muscle causing an apparent flaccid paralysis in the opponent is applied to all muscles. Such hurdles as pharyngeal paralysis are taken lightly with a brief reference to spasm in neck muscles. About seventy pages of the book is given over to a fairly straightforward exposition of the recommended treatment for different muscle groups, and this will form the most valuable part of the book for the reader who seriously attempts to apply the therapeutic measures outlined. The treatment in brief consists in the local use of heat to overcome "spasm" in the acute stage of the disease and then muscle training in an attempt by overcoming "mental alienation" to develop "coordination" and "mental awareness" in the conscious use of the apparently paralyzed muscles. Braces, casts and immobilization are decried. The exact number of patients treated in this country is not clearly stated, but is apparently rather small. None of the usual figures measuring the amount of residual paralysis are offered. No control studies are described. This is particularly unfortunate in a study of poliomyelitis in which unpredictable and spontaneous variations in paralysis are so well known. In fairness it must be remembered that the principles held "in orthodoxy," as the author states it, by orthopedists for many years and the routines used by them in treatment have been equally lacking in any critical study with controlled clinical observations. There can be little doubt that the author's work, if not the book itself, will stimulate a much needed re-evaluation of the after-care of the paralysis of this dreaded disease.

Communicable Disease Control. By Gaylord Anderson, M.D., and Margaret Arnstein, R.N. Price, $4.25. Pp. 434, with 13 tables. New York: The Macmillan Company, 1941.

This volume of 434 pages is written in simple style and will appeal to physicians and nurses engaged in public health work. Its object is to tell how to protect the general population, and for that reason it would not have the same appeal for the private practitioner, whose chief interest is in protecting individual patients. It is packed with information on the problems of a community's health. The authors tell how communicable diseases are stopped by isolation, quarantine and vector control and give the principles which should guide the health officer in matters of immunity. They endeavor to determine whether it would be worth while to expend vast sums of money for preventive control in given instances. It is interesting to note that they state that there is no evidence to indicate that the individual risk of infection from exposure to a carrier is but one tenth of that due to exposure to a person with the disease in an active phase. One dictum of Chapin is quoted which would appeal to all pediatricians, i. e., "A health department should require notifications of only those conditions about which it can or plans to do something."

The book considers the role of the public health nurse and some factors of home nursing and definitely states that it does not stress hospital care. It treats the diseases from an epidemiologic standpoint and points out how epidemics can

be studied. It then considers the various communicable diseases, including food poisonings, trichinosis, some cutaneous skin infections, such as impetigo, and some diseases spread by arthropods. The descriptions of the diseases are scanty at best and not sufficiently detailed to interest the clinician, but one should remember that the objective of the book is not to consider clinical detail but merely to cover the epidemiology, control and methods of protection against disease, procedures to be followed by health departments and similar matters. It does not pretend to cover symptomatology and diagnosis.

One wonders whether books of this kind would be of maximum interest to the clinician. In some instances the authors mention procedures of active and passive immunization and neglect to refer to some important methods of passive control under suggested readings, such as Hoyne's method of treating meningitis and Foshay's experiences with tularemia.

The volume gives one a better conception of some of the difficult problems that confront the health officer.

Symptoms in Diagnosis. By Jonathan Campbell Meakins, M. D. Price, $4. Pp. 296, with 62 illustrations. Boston: Little, Brown & Company, 1941.

This book should be of value to the student, teacher and practitioner alike, for it is both refreshing and stimulating. In recent years, it is one of the few books that has been written largely on the interpretation of those symptoms that can be determined from careful observation and inspection of the patient. Dr. Meakins has presented his material in a concise and understandable way. In the preface he states: "This is not a text which alone will lead any student or practitioner to an immediate diagnosis; it is hoped, rather, that it will act as a stimulus to analyse what symptoms the patient presents, whether in an acute or chronic disease. Through nigh on forty years of intensive study of disease at the bedside, I have gone through the whole gamut of diagnostic criteria. I early found that a patient's symptoms were really of more importance in beginning the investigation of a case than physical signs or laboratory findings."

The adverse influence that disease has on the factors which control the normal pattern of growth and development is well outlined in the chapter "Physical Characteristics of the Body."

The relationship of various diseases to the significant changes in the appearance of the skin and its appendages is described in another chapter.

Many excellent schematic diagrams are used to illustrate the value in diagnosis of the correct interpretation of the distribution of sensory disturbances.

The importance of symptoms of localizing value, such as vomiting, diarrhea and dyspnea, are mentioned as important leads to a final diagnosis, provided one understands the underlying physiologic and pathologic mechanisms.

In conclusion, the author points out the value of the correct interpretation of disturbances of general function, such as fatigue, exhaustion, sleep, insomnia and coma.

Since diagnosis in children is largely dependent on objective symptoms and on an appreciation of the chemical, physiologic and pathologic processes that are responsible for these changes, this book should be of interest to the pediatrician.

Endotracheal Anaesthesia. By Noel A. Gillespie, D.M., B.Ch., M.A. (Oxon.); D.A. (R.C.S. Eng.). Price, $4. Pp. 187, with 44 illustrations. Madison, Wis.: University of Wisconsin Press, 1941.

This fairly small book contains nine interesting chapters, a goodly number of illustrations and a valuable bibliography and index.

The subject covers the history of endotracheal anesthesia, its advantages and disadvantages, insufflation, description and care of equipment and apparatus for intubation, various methods of intubation with uses and abuses, miscellaneous technical considerations during induction, maintenance, recovery and sequelae, choice of route, and uses of intubation for purposes other than anesthesia. Dr. Gillespie covers the field with extreme thoroughness.

References are listed at the end of each chapter, and the bibliography is conveniently classified. The subject is presented in a comprehensive manner without verbosity. The author's enthusiastic defense of the method is balanced by his honesty in stressing the occasions on which not to use it (e. g. in operations in which either chamber of the eye is opened).

The chapter on intubation in operations on infants and children should be of special interest to pediatricians. The following facts are emphasized:

"The more skillful and experienced the anaesthetist, the less frequently will he be compelled to intubate. Endotracheal anaesthesia is seldom required in operations upon infants because of the following technical difficulties: The protective reflex of the glottis is extremely irritable because of need for liquids only. The epiglottis is longer and the larynx higher than in adults. The glottis is small. Infants are easily exhausted by the effort of overcoming resistance to respiration. The glottic reflex may still be present where the circulatory and respiratory systems show signs of intolerance to depth of anaesthesia."

This book should be in the library of every anesthetist and of others interested in anesthesiology.

Syphilis en zwangerschap. By Loe Ping Kian, M.D. Price not given. Pp. 313. Batavia, Java: Keng Po, 1941.

Of late years the great importance of efficient treatment of syphilis during pregnancy has come to be fully understood among obstetricians and pediatricians. The present work is a carefully considered study of a large number of Chinese and Indonesian women who were cared for at the clinic in Batavia. It is interesting to the American physician to learn that the incidence of syphilis in both of these groups of women in the Netherlands East Indies is considerably less than it is in two large American clinics in which large numbers of colored women are treated.

For diagnosis the Wassermann reaction is given the most weight but is controlled by the Sachs-Georgi, Kahn or Meinicke reaction. Among 1,381 Chinese women, syphilis was found in 105, or 7.6 per cent. Among 2,371 Indonesian women, syphilis was found in 145, or 6.1 per cent. The symptoms and the details of treatment are fully discussed. A tabulation at the end of the work indicates that the results of treatment were excellent. For example, in a group of 150 Chinese women the number of syphilitic children born of the wholly untreated mothers was 52 per cent while for those who were actively treated the incidence of syphilis in the children fell to zero. Similar results are shown in the Indonesian group. Indonesians, it is explained, are natives of the islands in the Netherlands East Indies, to whom this designation has been given.

The author of this excellent piece of work is a native of Java, and the thesis is being presented for his degree in medicine. In these days of assault on human liberty by the forces of totalitarianism, an American physician may hope that a people capable of producing work of this type in scientific medicine may retain their liberties under the enlightened Dutch rule rather than be stifled by the forces of darkness.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St, Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30–May 2, 1942.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: April 29-30, 1942.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. Leo S. Friedman, 3586 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrmann, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

MEDICAL SOCIETY OF THE COUNTY OF KINGS AND THE ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

MEDICAL SOCIETY OF THE DISTRICT OF COLUMBIA, SECTION ON PEDIATRICS

President: Dr. James M. Moser, 3751 Jenifer St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William A. Howard, 2222 Que St. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHERN CALIFORNIA AFFILIATES

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

OKLAHOMA CITY PEDIATRIC SOCIETY

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barda, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. Ellsmer L. Piper, 3708–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.